ANNEX 1

Horizon Europe (HORIZON)

Description of the action (DoA)

Part A

Part B

DESCRIPTION OF THE ACTION (PART A)

COVER PAGE

Part A of the Description of the Action (DoA) must be completed directly on the Portal Grant Preparation screens.

PROJECT *Grant Preparation (General Information screen) — Enter the info.*	
Project number:	101095436
Project name:	Optimise and predict antidepressant efficacy for patient with major depressive disorders using multi-omics analysis and AI-predictive tool
Project acronym:	OPADE
Call:	HORIZON-HLTH-2022-TOOL-11
Topic:	HORIZON-HLTH-2022-TOOL-11-01
Type of action:	HORIZON-RIA
Service:	HADEA/A/03
Project starting date:	fixed date: 1 December 2022
Project duration:	54 months

TABLE OF CONTENTS

PROJECT SUMMARY

Project summary

Grant Preparation (General Information screen) — Provide an overall description of your project (including context and overall objectives, planned activities and main achievements, and expected results and impacts (on target groups, change procedures, capacities, innovation etc)). This summary should give readers a clear idea of what your project is about.

Use the project summary from your proposal.

280M of people worldwide suffers from major depressive disorders (MDD). Although a well-populated therapeutic landscape of anti-depre280M of people worldwide suffers from major depressive disorders (MDD). Although a well-populated therapeutic landscape of anti-depressants, the number of patients in remission is particularly low with not more than 6% of the patients who benefit from the current therapeutic journey.
OPADE objective is to identify key biomarkers that support the decision-making process of the healthcare providers.
The project focuses on the microbiota – brain -axis which plays a major role in mental health and in particular MDD. Through clinical investigations, the consortium partners will study the combination between genetics, epigenetics, microbiome and inflammatory networks to:
- Establish patient profiles to predict and optimise the efficacy of the antidepressants prescribed with an increase in the remission rate and reduction of impairment of real-life functioning,
- Establish the possible correlation between neuroinflammatory indices, target indicators of the microbiome, metabolomics, immune-profile linked, epigenomic, enzymatic algorithms,
- Evaluate molecular and non-molecular biomarkers that may represent predictive indices of recurrence
- Discover new molecular targets for a personalised approach,
- Improve the diagnostic accuracy for primary prevention,
- Evaluate retrospectively, using accurate anamnesis, the onset of depressive symptoms in adolescence.
- Establish how much and to what extent do blood biomarkers correlate with other specific biomarkers
350 patients between 14 and 50 years will be recruited in 6 EU and international countries for 24 months. Real-time EEG and patient cognitive assessment will be collected with blood, stool and saliva samples. Results and analysis will be used to train the AI / ML predictive tool, the main outcome of the project. A patient empowerment tool will be deployed over the project duration.

LIST OF PARTICIPANTS

PARTICIPANTS

Grant Preparation (Beneficiaries screen) — Enter the info.

Number	Role	Short name	Legal name	Country	PIC
1	COO	EBRIS	FONDAZIONE EBRIS	IT	935386230
2	BEN	CEINGE	CEINGE BIOTECNOLOGIE AVANZATE SCARL	IT	999951564
3	BEN	EURECAT	FUNDACIO EURECAT	ES	928030235
4	BEN	PERSEUS BIOMICS	PERSEUS BIOMICS	BE	913627869
5	BEN	AIE	ARTIFICIAL INTELLIGENCE EXPERT SRL	RO	905269864
6	BEN	Mama Health	MAMA HEALTH TECHNOLOGIES GMBH	DE	886506281
7	BEN	PROTOBIOS	PROTOBIOS OU	EE	991346015
8	BEN	Cephalgo	CEPHALGO	FR	888675007
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10	BEN	FUS	FUNDACION UNIVERSITARIA SANITAS	CO	915801736

PARTICIPANTS

Grant Preparation (Beneficiaries screen) — Enter the info.

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12	BEN	Accare	STICHTING UNIVERSITAIRE EN ALGEMENE KINDER - EN JEUGDPSYCHIATRIE NOORD-NEDERLAND	NL	915115946
13	BEN	IDIBGI-CERCA	FUNDACIO INSTITUT D'INVESTIGACIO BIOMEDICA DE GIRONA DOCTOR JOSEP TRUETA	ES	997946477
14	BEN	IMU	ISTANBUL MEDIPOL UNIVERSITESI	TR	967774433

LIST OF WORK PACKAGES

Work packages

Grant Preparation (Work Packages screen) — Enter the info.

Work Package No	Work Package name	Lead Beneficiary	Effort (Person-Months)	Start Month	End Month	Deliverables
WP1	Observational clinical trial management	1 - EBRIS	110.00	1	54	D1.1 – Documents submitted to competent authorities to initiate the adult and child clinical trials D1.2 – eCRF Validation Report, eCRF Release Report D1.3 – Mid-term recruitment report (paediatric & adult trials) D1.4 – Final recruitment report (paediatric and adult trials) D1.5 – Report on the status of posting results
WP2	Cognitive, psychopathological and non molecular biomarkers assessment	8 - Cephalgo	393.00	6	48	D2.1 – Report on patient socio-demographic and clinical anamnestic assessment D2.2 – Report on patient phsycopathological aspects D2.3 – Report on patient functioning and quality of life D2.4 – Report on patient resistance to treatment D2.5 – Report on patient EEG monitoring D2.6 – Global report on non-biological biomarkers
WP3	Molecular biomarkers quantification	7 - PROTOBIOS	257.00	1	54	D3.1 – Report on analysis of inflammatory markers and growth factors D3.2 – Report on metabolomic analysis D3.3 – Report on analysis of lipoprotein profile

Work packages

Grant Preparation (Work Packages screen) — Enter the info.

Work Package No	Work Package name	Lead Beneficiary	Effort (Person-Months)	Start Month	End Month	Deliverables
						D3.4 – Report on microbiome analysis D3.5 – Report on transcriptomics analysis D3.6 – Report on epigenomic and genomic analysis D3.7 – Report on pharmacogenetic and long QT phenotype D3.8 – Report on hormonal analysis D3.9 – Report on immuno-profiling by MVA D3.10 – Report on biological biomarkers D3.11 – Final repository of the OPADE biobank
WP4	Development and deployment of digital and tracking tools	6 - Mama Health	232.00	6	54	D4.1 – Final report including set up of the tool and on patient support session D4.2 – Report on data integration and validation D4.3 – First version on the AI-powered predictive tool D4.4 – Report on the development of the AI-powered predictive tool D4.5 – Report on the regulatory status of the AI-predictive tool
WP5	Dissemination and communication activities. Exploitation strategies	9 - BIOKERALTY	78.00	1	54	D5.1 – Dissemination, communication & exploitation plan D5.2 – Project dedicated public website D5.3 – Interim dissemination, communication & exploitation plan 1 D5.4 – Interim dissemination, communication & exploitation plan 2

Work packages

Grant Preparation (Work Packages screen) — Enter the info.

Work Package No	Work Package name	Lead Beneficiary	Effort (Person-Months)	Start Month	End Month	Deliverables
						D5.5 – Final dissemination, communication & exploitation plan D5.6 – Clinical guidelines analysis and update D5.7 – Report on events with stakeholders D5.8 – Report on IPR generated over the project and future exploitation strategy
WP6	Project management activities	1 - EBRIS	67.00	1	54	D6.1 – Project Quality Handbook D6.2 – Data Management Plan (DMP)
WP7	Ethics requirements	1 - EBRIS	0.00	1	54	D7.1 – OEI - Requirement No. 1 D7.2 – OEI - Requirement No. 2 D7.3 – OEI - Requirement No. 3 D7.4 – OEI - Requirement No. 4

Work package WP1 – Observational clinical trial management

Work Package Number	WP1	Lead Beneficiary	1. EBRIS
Work Package Name	Observational clinical trial management		
Start Month	1	End Month	54

Objectives
The objective of this WP to initiate and follow-up the observational OPADE clinical trial. EBRIS will coordinate the efforts and work with an expert in clinical trials to ensure that GCPs (good clinical practices) are implemented.

Description
Task 1.1: Clinical trial documents preparation and submission (lead: EBRIS, contrib: FUS, UNISI, ACCARE, IDIBGI-CERCA, IMU) EBRIS will centralise information from the different clinical partners to submit the study protocol, informed consent form and other regulatory documents to National Competent Authorities (NCA) and local ethics committees to get the approval to initiate the clinical study. We will translate the clinical study protocol synopsis and study documents for patients in the local languages. We will activate insurance policies per local requirements. We will prepare, review and finalise study plans and specific work instructions for Investigators in compliance with the study protocol and GCP guidelines. We will arrange financial and quality agreements between the parties involved. Task 1.2: Electronic data capture system implementation (lead: EBRIS, contrib: contrib: FUS, UNISI, ACCARE, IDIBGI-CERCA, IMU)) We will design, review and finalise the Case Report Form (CRF) according to the study protocol and ensure that all data are collected in the same way for each clinical centre. We will design the database and implement the eCRF according to the approved study CRF, protocol specifications and OPADE partner requests. Data will be backed-up twice daily (two weeks of storage), physical and logical procedures and controls will be applied during the entire duration of the projects to ensure the safety of electronic records in compliance with GDPR, current laws and regulations. The eClinical system will pseudonymise patient data and biological samples and perform the treatment blind assessment as described in section 1.2. Task 1.3 Data collection & validation (lead: EBRIS, contrib: contrib: FUS, UNISI, ACCARE, IDIBGI-CERCA, IMU)) OPADE investigators will screen and identify eligible patients to enter the clinical trial. Throughout the study duration, data entered will be subject to automatic quality control checks (e.g., real-time feedback for site staff as they enter data) for completeness and accuracy. The study data manager will perform manual quality control checks or through real time reports and routine statistical validity checks, at an agreed and regular interval. This will identify missing or suspect entries. An electronic audit trail will be available. All staff involved with the trial will undertake the appropriate generic, GCP and trial-specific training to ensure that they meet the specific requirements of the trial. Task 1.4 Study closure and Final report (lead: EBRIS, contrib: FUS, UNISI, ACCARE, IDIBGI-CERCA, IMU)) Once the trial has finished, the final, cleaned databases will be locked and archived for audit and storage by DB lock procedures. These data will be maintained for the period reported in the trial protocol and records will be archived according to archiving procedures. The final reconciled, cleaned database when locked, will be transferred to the study statistician for data analysis according to the Statistical Analysis Plan approved. The statistician will prepare a final integrated clinical/statistical report at the end of the study. We will submit study results to CA and Ethics Committees, published them in scientific journals and present at scientific congresses. Any formal publication of study results will be a collaborative effort between parties involved (dissemination WP5).

Work package WP2 – Cognitive, psychopathological and non molecular biomarkers assessment

Work Package Number	WP2	Lead Beneficiary	8. Cephalgo
Work Package Name	Cognitive, psychopathological and non molecular biomarkers assessment		
Start Month	6	End Month	48

Objectives
The objectives of this WP are to collect clinical anamnestic and cognitive status of the patient to include

Description
Task 2.1– Socio-demographic and clinical anamnestic assessment (lead: UNISI, contrib: FUS, ACCARE, IDIBGI-CERCA, IMU) Before the start of the clinical trials, the clinical partners will agree on the information that need to be collected during the course of the clinical trial and will provide a form that all OPADE clinical centres will have to use (mandatory). We will collect the socio-demographic information (age, gender, race, education, employment status, housing status, financial strain, education level, marital status, social support, age of disease onset, illness course, pharmacological treatment, food patterns. All available sources of information (patient, family, medical records and mental health workers) will be used to complete the form. Information will be collected at the day of the enrolment and updated over follow-up (104 weeks). Task 2.2- Assessment of psychopathological aspects (lead: UNISI, contrib: FUS, ACCARE, IDIBGI-CERCA, IMU) At each visit, OPADE clinical centres will assess the psychopathological aspects of the patient using existing and clinically approved questionnaires. All centres will use the same version of the form to ensure a smooth data collection and harmonisation. The Hamilton Rating Scale for Depression (HAM-D) includes multiple-items and is used to provide an indication of depression, and as a guide to evaluate recovery. It is designed for adults and allows to rate the severity of their depression by probing mood, feelings of guilt, suicide ideation, insomnia, agitation or retardation, anxiety, weight loss, and somatic symptoms. The Beck Depression Inventory-Second Edition (BDI-II) is a widely used self-report inventory measuring the severity of depression in adolescents & adults, based on a 2-week time period. The BDI-II is widely used as an indicator of the severity of depression and validity across different populations and cultural groups. The Montgomery–Åsberg Depression Rating Scale (MADRS) is a diagnostic questionnaire usually used to measure the severity of depressive episodes in patients with mood disorders. It is more sensitive to the changes brought on by antidepressants and other forms of treatment than the Hamilton Scale. Mood Spectrum-Self Report-Current (Mood_SR_C, Mood_SR last month) is a psychometrically questionnaire evaluating the presence of a wide range of features of mood psychopathology. These features include the DSM core symptoms of depression and mania, subthreshold manifestations, mood-related personality traits, prodromal and residual symptoms, and behaviours associated with – or arisen as a means of coping with – mood disorders. Task 2.3 - Assessment of functioning in real life and quality of fife (lead: UNISI, contrib: FUS, ACCARE, IDIBGI-CERCA, IMU) We will assess the functioning in real life and quality of life of MDD patients. We will use existing scales. All clinical partners will use the same version to smooth data harmonisation and analysis. The form will be completed by the patient at each visit. Global Assessment of Functioning (GAF) scores the severity of illness for Adults – Recognised worldwide . It is constructed as a global measure and rates psychological, social, and occupational functioning. GAF recorded values can be either a single score (only the most severe of the symptom and functioning values is recorded) or separate scores for symptoms (GAF-S) and functioning (GAF-F). For both the GAF-S and GAF-F scales, there are 100 scoring possibilities (1-100). The level of functioning for teenagers will be measured with the Childhood Global Assessment Scale (CGAS). Social and role functioning are specifically assessed to obtain differential measures and provide clinician-rated single overall scores that take age and phase of illness into account. This enables social and role functioning to be studied as independent domains not confounded by clinical symptoms. GF: Social assesses quantity and quality of peer relationships, level of peer conflict, age- For both scales, scores range from 1 to 10, with 1 indicating extreme dysfunction and 10 indicating superior functioning. Short form 36 adult form (SF36) is a short questionnaire with 36 items which measure multi variables: physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, mental health, energy and vitality, pain, and general perception of health. For each variable item scores are coded, summed, and transformed on to a scale from 0 (worst possible health state measured by the questionnaire) to 100 (best possible health state). The Pediatric Quality of Life Inventory (PedsQL) is a generic health status instrument with parent and child forms that assesses five domains of health (physical functioning, emotional functioning, psychosocial functioning, social functioning, and school functioning) in children and adolescents. Task 2.4 – Evaluate resistance to treatment (lead: UNISI, contrib: FUS, ACCARE, IDIBGI-CERCA, IMU) We will use the Antidepressant Treatment Record (ATR) form that is sensitive and specific in its ability to identify

treatment resistance levels ranging in adolescents with MDD. It assesses a score on previous treatments, duration and failure. The form will be completed by the patient at each visit.
Task 2.5 - Real time patient monitoring via EEG (lead: CEPHALGO , contributors: UNISI, FUS, ACCARE, IDIBGI-CERCA, IMU)
The task will provide real time patient monitoring via electroencephalography and the consequent emotion analysis via convolutional neural network. CP proposes three major offers:
1)EEG signal acquisition: depending on patients' pathologies and difficulties in identifying own emotions according to the evaluations from their psychiatrists, CP classifies the patients into groups with sub-classifications such as sex/ gender, age, culture, etc. Each group of patients will be instructed how to wear the EEG device during daily life, on average 8 - 10 hours per day.
2)Patients' self labelling of emotions: each group of patients will be instructed how to conduct their self labelling of emotions on the mobile application, both instant emotion feedback and the one after reviewing the emotion analysis of CP. The emotion feedback consists of two indicators, valence and arousal levels, both range from 1-9 and represent mental positiveness and activation, respectively. Considering the different characteristics in brainwaves across patients in different groups, the patients are encouraged to note their emotions as frequently as possible, ideally every 15 - 30 minutes for a period of 7-14 days, as the reference period. This period serves as a personal reference for each patient and with this reference, CP's convolutional neural network is able to choose the most adequate algorithm for this patient and train this algorithm particular for this patient, reaching the most optimised prediction for the subject-dependent algorithm. During this reference period, the patients will not be able to see the emotion analysis to avoid the possible frustration due to the inadequate assignment of algorithm.
3)Introducing variants into algorithms: even though the patients are encouraged and reminded to note their emotion, whether the patient will conduct this self labelling as frequently as requested is one variable. This frequency is considered to be a part of an indicator of the patient's self engagement in the treatment/assignment. In addition, patients in each group will be assigned to different relaxation exercises and while they conduct such exercises, their brainwaves will be recorded to observe the effect of individual relaxation exercises on the given groups of patients. … Overall, the variants of CP are frequency of self labelling, types of relaxation exercises, and durations of reference periods over patient's status (pathologies, difficulty in emotion recognition, age, gender, culture, etc).
4)Feedback to patients: with the precedent steps, CP is able to derive the variants that influence the patients' treatment effectiveness both qualitatively and quantitatively with the bioindicator EEG. The concluded variants will be then provided to the psychiatrists and medical professionals within OPADE to be used to adjust or to pilot the treatment of the said patients. This final step together with the precedent steps form a complete cycle of psychotherapy, focusing on the effectiveness of molecules within antidepressant throughout OPADE.

Work package WP3 – Molecular biomarkers quantification

Work Package Number	WP3	**Lead Beneficiary**	7. PROTOBIOS
Work Package Name	Molecular biomarkers quantification		
Start Month	1	**End Month**	54

Objectives
This WP covers the multi-omic analysis that will be performed on patient samples (blood/stool). The objective of this WP, beside the bench analysis of the samples consists in correlated the obtained results, using AI and ML, to dress a patient pattern in response to the considered antidepressants, in the teenager / young adult.

Description
Task 3.1: Analysis of inflammatory markers and growth factors in patient plasma samples to evaluate patient response to treatment and investigate predictive efficacy (lead: EURECAT, contrib: UNISI, FUS, ACCARE, IDIBGI-CERCA, IMU) The task will analyse and evaluate several inflammatory markers such as G-CSF, GM-CSF, IFN-γ, IL-10, IL-12p40, IL-15, IL-1α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8/CXCL8, MCP-1/CCL2, TNF-α, TNF-β/Lymphotoxin-a. The analysis will be carried out using multiplexed immunoassays. The use of magnetic beads for the quantification of several molecules in one run will decrease the amount of sample needed for these analyses and avoid possible plate-to-plate or batch errors. Task 3.2: Metabolomic analysis in patient plasma samples to analyse the response to antidepressant (lead: EURECAT, contrib: UNISI, FUS, ACCARE, IDIBGI-CERCA, IMU)

Different analytical methods will be developed and optimized using liquid chromatography coupled to triple quadrupole mass spectrometry to cover a wide range of metabolites pathways to explore the response of patients to the antidepressant. The metabolomics analysis will involve three different groups of metabolites: 1) Tryptophan metabolism intermediates (tryptophan, serotonin, 5-HIAA, kynurenine, kynurenic acid and other hormones and derivatives involved in the pathway) and other purine-related compounds (paraxanthine/xanthine ratio); 2) L-acylcarnitines (including short-, medium- and long-chain acylcarnitines), paying special attention to laurylcarnitine and acetylcarnitine; 3) Phenolic (and related) compounds, such as phenolic acid, mandelic acid or methoxy-hydroxyphenyl-glycol.

Task 3.3: Analysis of lipoprotein profile in patient plasma samples (lead: EURECAT, contributors: UNISI, FUS, ACCARE, IDIBGI-CERCA, IMU)

The task will evaluate several forms of lipoproteins: Apolipoprotein A1 and A2, HDL-apolipoprotein A1 and A2, HDL3-free cholesterol, HDL3-apolipoprotein A1, HDL2-apolipoprotein A2, apolipoprotein A2, IDL, HDL-apolipoprotein A2, VLDL and its subtypes, VLDL2-triglycerides, VLDL3-triglycerides, VLDL2-cholesterol, VLDL3-cholesterol, VLDL4-cholesterol, VLDL4-free cholesterol, VLDL2-phospholipids, VLDL3-phospholipids, LDL5-cholesterol, LDL5-free cholesterol, LDL5-phospholipids, LDL5-apolipoproteinB, HDL3-cholesterol, HDL4-cholesterol, HDL3-free cholesterol, HDL4-free cholesterol, HDL3-phospholipids, HDL4-phospholipids, HDL3-apolipoprotein A1, HDL4-apolipoprotein A1, HDL3-apolipoprotein A2 and HDL4-apolipoprotein A2. For this purpose, we will use the 1H-NMR platform working with the Car-Purcell-Meiboom-Gill (CPMG) pulse sequences for the measurement of dynamic processes, which is very useful to identify small molecules in the presence of large proteins and lipoproteins.

Task 3.4 – Microbiome analysis in patient stool and impact on treatment (lead: PERSEUS BIOMICS, contrib: UNISI, FUS, ACCARE, IDIBGI-CERCA, IMU)

Patient whole gut microbiome analysis will be conducted at multiple points within the study through PERSEUS BIOMICS DynaMAP analysis, uncovering the bacterial and fungal components of the patient gut microbiome. Particular strain level analysis screening will be conducted for the presence of the microbiome-depression related bacterial species, such as the recently described potential causal effect of Morganella on major depressive disorder. Nat Genet 54, 134–142 (2022). In view of recent developments, dietary consideration versus metabolomic potential of the microorganisms will be included in the analysis.

Task 3.5: Transcriptomics analysis in patient plasma samples to determine patient response to treatment (lead: EBRIS, contrib: CEINGE, UNISI, FUS, ACCARE, IDIBGI-CERCA, IMU)

1/ plasma RNA extraction: Total RNA, including miRNAs, is isolated using a commercial kit (miRNeasy Mini Kit, Qiagen). RNA concentration is assessed using a spectrophotometer. 2/miRNAs expression assay: The nCounter miRNA Expression Assay (NanoString Technologies) is designed to provide an ultra-sensitive, reproducible, and highly multiplexed method for detecting miRNAs in total RNA across all biological levels of expression without the use of reverse transcription or amplification. The assay can be run on total RNA isolated from liquid biopsy. NanoString technology is based on the direct molecular barcoding and digital detection of target miRNAs using a colour-coded probe pair. Excess probes are washed using a 2-steps magnetic bead-based purification.

Task 3.6 Epigenomic and genomic analysis to evaluate response to treatment (lead: CEINGE, contrib: EBRIS, UNISI, FUS, ACCARE, IDIBGI-CERCA, IMU)

We will perform methylome analyses on genomic DNA extracted by blood and saliva. Methodologic approach will consist in Epic Array Illumina interrogating the methylation state of 850.000 CpG sites per sample. We will run bioinformatic analysis by RnBeads R-based scripts (1,2). As a first step quality score will be determined. According to sample annotations, batch effects and phenotype covariates will be identified. DNA methylation distributions will analyzed and intergroup as well as intragroup variability in methylation profiles is quantified. Furthermore, differential methylation between groups of samples will be characterized. Differentially methylated CpG sites, promoters and CpG island will be calculated among single samples and among groups by Mann Withney tests and heatmaps will be generated. According to the dissimilarities in terms of DNA methylation at each of the 850k CpG sites a Principal Component Analysis (PCA) will be performed and PCA plots will be generated.

Genetic variants will be identified by using an ad hoc NGS panel. Moreover, depression related genes and CpG sites will be bioinformatically extracted from the above whole genome analyses to perform straight forward cross analyses among all the here proposed biomarkers.

Task 3.7 Pharmacogenetic and long QT phenotype (lead: IDIBGI-CERCA , contrib: CEINGE, UNISI, FUS, ACCARE, IDIBGI-CERCA , IMU)

Genetic analysis will be conducted through a saliva sample. Cardiovascular risk factors will be obtained through a blood sample, electrocardiogramme and data extracted from clinical records (BMI, weigh and high). Sociodemographics, clinical and social functioning outcomes (UKU, UFS, Cognitive scales) QoL, and lifestyle will be self-reported by patients.

Task 3.8 Hormonal analysis: cortisol quantification to determine treatment efficacy and develop predictive model (lead: EBRIS, contrib: UNISI, FUS, ACCARE, IDIBGI-CERCA, IMU)

Patient saliva sample is harvested to perform cortisol quantification using a radioimmunoassay technique. Saliva sample

is incubated with tracer for 30 min at 37°C. The detection is done using gamma-counter. The lower detection limits of the assay are 0.8 nmol/l.
Task 3.9 Immuno-profiling by MVA (lead: PROTOBIOS , contrib: UNISI, FUS, ACCARE , IDIBGI-CERCA, IMU)
This task will involve generation of antigen repertoires of MDD and across drug-treatment groups. The plasma samples from clinical study cohorts will be subjected to high-throughput antibody epitope profiling (immunoprofiling by MVA). We will then perform data analysis and expectedly generate antibody epitope panels associated with the MDD disease and specific treatments. These studies will contribute to development of novel biomarkers of personalized MDD treatment response.
Task 3.10 Management of the biobank (lead; EBRIS, contrib: CEINGE, EURECAT, PERSEUS BIOMICS, PROTOBIOS, FUS, UNISI, ACCARE, IDIBGI-CERCA, IMU)
This task will set up the biobank required to run the project studies. The project will collect biosamples (blood, stool, saliva) from 350 patients (observational study). The biobank will therefore include 1750 biosamples of each type i.e. over 5250 biosamples. EBRIS will be managing the biobank in its facilities as follows:
- The sample is dropped or shipped refrigerated at the relevant recruitment centre (FUS, UNISI, ACCARE, IDIBGI-CERCA, IMU)
- The centre centrifuges the blood and stores serum, blood cellular components, stools & saliva at -20°C
- Every 2 months, samples are pooled and shipped to EBRIS for biobanking
- EBRIS receives the samples that are barcoded and stored
- EBRIS manages the samples with a dedicated biobanking software (Freezerworks)
- EBRIS distributes the samples to the partners in charge of the omic analysis (PERSEUS BIOMICS, PROTOBIOS, CEINGE, EBRIS, EURECAT)
EBRIS will also be responsible for maintaining the biobank and making it accessible to other research project after the completion of this project. The biobank will be open to other researchers, subject to approval to an internal committee that will evaluate the scientifically validity of the request.

Work package WP4 – Development and deployment of digital and tracking tools

Work Package Number	WP4	**Lead Beneficiary**	6. Mama Health
Work Package Name	Development and deployment of digital and tracking tools		
Start Month	6	**End Month**	54

Objectives
The objectives of this WP are: - To deploy the patient empowerment tool during the clinical trial - To develop and validate the OPADE AI-powered predictive tool

Description
Task 4.1: Deployment of a digital tool for patient community engagement (lead: MAMA HEALTH , contrib, UNISI, ACCARE, FUS, IDIBGI-CERCA, IMU) This task will provide a full patient engagement and empowerment solution, to keep them close to the study and empower them with the experience of others. MAMA HEALTH will offer 3 key solutions: 1)Patient engagement: starting when the first 10 patients are onboarded in the OPADE study, patients will be invited to moderated peer-to-peer sessions. They will exchange support and learn from the experience of others. MAMA HEALTH will offer the digital environment and the moderation of those sessions with professional personnel. The frequency of the sessions will be set up based on the recruitment rate of the study. 2)Data collection: in the same time frame, MAMA HEALTH offers an innovative solution to capture patient-reported stories and outcomes. This will be deployed in the form of a chatbot that patients will use to share their stories retrospectively and keep their story up to date during the duration of the OPADE study. The chatbot will require a one-time initial workshop to customise the tool for the objectives of this study. Data will be processed and stored following GDPR requirements. 3)Data processing and mining: with the patient-reported data captured through the chatbot, MAMA HEALTH will use its proprietary technology to extract key information and mine the journey of the patient population. This activity will take place in the second half of the study.

Task 4.2: Data integration, storage, and harmonization (lead: AIE, contrib: EBRIS, EURECAT, CEINGE, PERSEUS BIOMICS, PROTOBIOS)

From a Data Sciences point of view, the collected data are heterogeneous – structured, unstructured, time-course, molecular, signals, etc. – and, and will have many versions. We want the data to be in the same place as the tools for their analysis. Thus, we will upload and store the data into a cloud (e.g., Amazon AWS) Data Lake. As the data is continuously collected and produced as a result of various processing it will have different versions. We will use special DataOPS (Data Operations) techniques/software (e.g., dbt) to track their entire life cycle. All the raw data should be transformed into the formats required by the various AI/ML algorithms that we will use. For this, we will develop various software tools, like bioinformatics and signal processing pipelines for molecular and EEG data, respectively. We will also follow the new trend – feature store. Features are inputs to ML/AI models used during training and inference. An example is Amazon SageMaker Feature Store, a fully managed, purpose-built repository to store, share, and manage features for machine learning (ML) models.

Task 4.3: Automate the AI-powered data-driven research in the field (lead: AIE, contrib: EBRIS, EURECAT, PERSEUS BIOMICS, PROTOBIOS)

We will formulate the project goals as Data Science problems, from the beginning. Using tools like bcbio-nextgen (https://github.com/bcbio/bcbio-nextgen) and others, we will develop/implement automated bioinformatics pipelines to pre-process molecular data (omics, etc.) and transform them in the format required by the AI/ML algorithms. From these data, Robotic Process Automation will form the required input-output pairs, e.g., circulating miRNA as input and responder or non-responder to a certain treatment.. The AutoML/AI algorithms inside Python packages like TPOT (http://epistasislab.github.io/tpot/), Pycaret (https://pycaret.org/), AutoGluon (http: https://auto.gluon.ai/), Autokeras (https://autokeras.com/), etc., will be applied to the data to develop predictive models. Generally, AutoML are low-code platform helping experienced teams to perform and manage experiments faster, easier and better, and to avoid code errors. Explainable AI (XAI; https://christophm.github.io/interpretable-ml-book/) will be used to make models' predictions transparent, and understandable by biomedical teams and to discover the relevant inputs (e.g., biomarkers) and their relative importance at the population (cohort), group (possible stratification) and individual (personalized) level. We will use SHAP method together with ExplainerDashboard. The last package has a facility allowing us to simulate the correction of the personalized altered biomarkers, to see e.g., what correction could transform a non-responder into a responder to certain treatments. The predictions will be expressed as "If-Then" conditional rules, by using the Anchors XAI method. Moreover, we will transform the predictive rules into the prescriptive format, meaning that the predicted results will be paired with clear recommendations for the physicians – which is the best action/decision for a particular patient in a given health state. The recommendations will be based on the best practice guidelines. For the time-course data and signals, we will use statistical and AI/ML methods specific for time-series e.g., the Python package Prophet (https://facebook.github.io/prophet/), 1-D Convolution Neural Networks, and also the algorithm developed by AIE (RODES – Reversing Ordinary Differential Equations Systems). RODES automatically discovers differential equations models from time course data, using Symbolic Regression Genetic Programming. The system of differential equations will be meaningful in a pharmacological framework, modelling the pharmacokinetics and pharmacodynamics of the investigated depression drugs.

Task 4.4: Develop, Implement and Validate the OPADE predictive tools (lead: AIE, contrib: EBRIS, PERSEUS BIOMICS, EURECAT, PROTOBIOS)

Using the platform developed in the previous task in the cloud we will develop the predictive tools of the OPADE project. We want the tools to be cost-effective ensuring a commercial success. This means we want to achieve the highest possible performance at a minimum cost. Generally speaking, we have multiple categories of measurements, and we want to reduce them incrementally based on developing predictive models for an increasing number of patients. At each modelling iteration, the performance will be assessed, and the relative importance of various inputs will be checked. As a result, we will eliminate only the uninformative measurements, without sacrificing the performance. It is important to mention that, due to the high functional redundancy of the molecular networks and pathways, feature selection based on inputs correlations, should be avois, as the lead to models not generalyzing well to new cohorts. The noisy inputs will be eliminated using perturbation methods. This will not eliminate highly correlated inputs if they are relevant.

We will also check the representativeness of the cohort for the target population. This is done by partitioning the data into training and testing sets (e.g., 75/25%) and running the algorithms multiple times, such as different cases go in the two sets. A large performance variability (instability) indicates that the ratio between the number of patients and the number of inputs is too small, and we need more patients and fewer inputs. We expect the instability to decrease as at each iteration we are improving this ratio. We will end up with highly performant, robust, clinically validated predictive tools for early diagnosis, treatment drugs, and dosage regimens selection, response prediction, and monitoring.

Task 4.5: Prepare regulatory validation of the AI-powered digital tool (lead: AIE, contributors: EBRIS, BIOKERALTY)

The AIE team will prepare the documentation required to solve the regulatory issues in collaboration with the contributor partners. As we target an international market, especially the EU and US, we will need both EC Mark and FDA approval. We will closely follow the evolution of the regulatory landscape as it is changing toward facilitating the AI/ML software

functioning as medical devices, and we intend to benefit from this trend. We will use any means to accelerate the regulatory approval, for example, applying for FDA Breakthrough Devices qualification.

Work package WP5 – Dissemination and communication activities. Exploitation strategies

Work Package Number	WP5	Lead Beneficiary	9. BIOKERALTY
Work Package Name	Dissemination and communication activities. Exploitation strategies		
Start Month	1	End Month	54

Objectives

This WP covers the strategies to i) inform about the project and its results, ii) distribute and make the results available and iii) make use of its results. The objectives of this WP are:
• Formulate a Dissemination and Communication Plan, which disseminates its results by the most appropriate means and promotes the project throughout its duration, showing the benefits it brings to society as a whole.
• Clinical guidelines analysis and update.
• Ensure stakeholder engagement in the research process to improve the translation of research results.
• Formulate an IPR and Exploitation plan.

Description

Task 5.1 Communication strategy development (lead: BIOKERALTY, contrib: All)
BIOKERALTY will identify the best offline and online communication channels to target the audiences pre-defined audiences (regulators, key opinion leaders (KOLs), scientists). BIOKERALTY will develop the project branding (website, logo, communication media supports). BIOKERALTY will coordinate researcher video interviews and photographic project coverage for promoting the project to the general public, non-governmental organisations and regulator/policy makers. BIOKERALTY will supervise and coordinate partner communication strategies. The communication plan will be evaluated and tuned continuously during the project.
Task 5.2 Dissemination activities (lead: BIOKERALTY, contrib: All)
BIOKERALTY will propose to OPADE partners the list of key events to reach their peers, industry leader and regulators through oral presentations and congresses. The dissemination plan will be yearly updated with the list of events for each year. BIOKERALTY will prepare an internal repository with the presentations and posters presented at the events and will make them available on opade.eu website.
Task 5.3 Existing clinical practice guidelines (CPG) analysis and opportunities to develop new ones (lead: BIOKERALTY, contributors: All)
This sequential process begins with the delimitation of the subject matter of the CPG. It continues with the formation of the CPG development group. This is followed by formulating the clinical questions, searching for and reviewing the evidence, evaluating and synthesising the evidence, and conducting an external review. Finally, it is necessary to consider aspects of editing, dissemination and updating of the CPG. BIOKERALTY will analyse the existing clinical guidelines regarding the management of MDD and coordinate discussions with KOLs (from OPADE and external) to write updated / new clinical guidelines based on OPADE outcomes including but not limited to, set of biomarkers of interest, mood tracker analysis…
Task 5.4 Stakeholder workshops and webinars for cross-project opportunities (lead: BIOKERALTY, contrib: All)
BIOKERALTY will organise online webinars with the MDD actors including but not limited to hospitals, psychiatry centres, general practitioners, and patient associations to present the outcome of the project. BIOKERALTY will identify and reach out to other EU-funded projects working on similar topics (psychiatry, gut-brain-axis…). Gathered with the final even of the consortium, BIOKERALTY will organise a face-to-face event and invite OPADE external stakeholders to present the final project outcome and the envisaged long term impacts.
Task 5.5 Innovation management (lead: EBRIS, contrib: All)
All over project duration, the consortium will review the exploitable assets and their associated IP, under the lead of EBRIS. New IP will be protected for future exploitation. Business plans will be updated based on the outcomes. After the result classification by innovation and market potential, the IPR will be assessed from the freedom to operate perspective. The IPR assessment will aim to, among others: 1) identification of the background IPR involved in the Project, as to the information provided by the Partners; 2) arrangement of the IP issues within the consortium agreement; 3) identify and classify the key exploitable results , foreground and side ground IPRs and determine their optimum ways of protection, such as: registrable IPRs associated to the key exploitable results (e.g. patents, registered designs and others); trademarks

(names and logos associated to the Project); copyrights (especially, those dealing with articles and scientific materials, computers programs and software, marketing materials and the like); database rights (protection for collections and compilations of data); trade secrets (e.g. confidential business information, associated know-how); 4) Coordinate the patentability study and the registration of the patentable key exploitable results, to be performed by an international patent attorney firm. The following work methodology will be performed in order to achieve the above mentioned goals, where appropriate: periodical face-to-face and remote interviews during the OPADE project lifetime; establishing the IP contact persons of each Partner and configuration of the IPR management bodies; control of the periodical update of the IPR repository on the basis of the information provided by the Partners; coordination with external agents (e.g. patent attorney firm); assessment on the distribution strategy of the protected elements.
Task 5.6 Exploitation strategies and updated business plans (lead: EBRIS, contrib: MAMA HEALTH, PROTOBIOS, CEPHALGO, AIE, PERSEUS BIOMICS)
EBRIS will keep a repository of the exploitable assets identified over PROTOBIOS project duration. Risks and potential obstacles to commercialisation will be assessed and business plans created / updated. OPADE project includes a broad range of exploitable assets from start that are carried on by different privates organisations / SMEs. EBRIS will ease the IP discussions within the consortium to make sure that the developed products reach the patients shortly after the project end.

Work package WP6 – Project management activities

Work Package Number	WP6	**Lead Beneficiary**	1. EBRIS
Work Package Name	Project management activities		
Start Month	1	**End Month**	54

Objectives

• To carry out the management, co-ordination and reporting activities necessary to:
• Implement the project management principles described in the Project Management section
• Ensure effective implementation of the project in line with guidelines from the Commission, the Project Contract and the Consortium Agreement.

Description

This work package covers the activities of the Project Coordinator (EBRIS) in managing the consortium. Management activities must be adapted to the needs of the project as it evolves, but will include at least:
• Organize communication between the Consortium and the Commission
• Set up and run financial accounting and budget reporting processes within the Consortium
• Coordinate progress reporting within the Consortium by work package Leaders, and between the Coordinator and the Commission.
• Monitor the progress of individual work packages, in terms of production of deliverables according to schedule, and other key indicators of progress.
• Continuously monitor significant project risks: identify, assess probability and consequences, and devise mitigation strategies.
• Deal with any conflicts which may arise between project participants (in accordance with the principles defined in the Project Management section
• Propose any modifications in the project plan which might be necessary in the light of experience in actually running the project, or due to factors external to the project. Carry out the formal steps needed to obtain approval by Consortium members and the Commission.
• Constitute and run the project management bodies defined in the Project Management section
• Organize and run Project Reviews.
Please note that this WP only relates to consortium coordination and interaction with the EC project officer, which is the responsibility of the coordinator (EBRIS). It does not include the technical coordination of individual work package or the attendance to consortium meetings, which is already factored in individual work packages. A full-time project manager will be appointed from EBRIS. All other OPADE beneficiaries have allocated 1PM to support the reporting of financial information at each of the period and their presence at the periodic reviews.

Work package WP7 – Ethics requirements

Work Package Number	WP7	Lead Beneficiary	1. EBRIS
Work Package Name	Ethics requirements		
Start Month	1	End Month	54

Objectives
The objective is to ensure compliance with the 'ethics requirements' set out in this work package.

Description
This work package sets out the 'ethics requirements' that the project must comply with.

STAFF EFFORT

Staff effort per participant

Grant Preparation (Work packages - Effort screen) — Enter the info.

Participant	WP1	WP2	WP3	WP4	WP5	WP6	WP7	Total Person-Months
1 - EBRIS	60.00	3.00	40.00	10.00	22.00	54.00		189.00
2 - CEINGE			40.00	4.00	1.00	1.00		46.00
3 - EURECAT			72.00	4.00	5.00	1.00		82.00
4 - PERSEUS BIOMICS			25.00	4.00	1.00	1.00		31.00
5 - AIE		10.00	10.00	120.00	1.00	1.00		142.00
6 - Mama Health				66.00	1.00	1.00		68.00
7 - PROTOBIOS			60.00	4.00	1.00	1.00		66.00
8 - Cephalgo		45.00		5.00	1.00	1.00		52.00
9 - BIOKERALTY					35.00	1.00		36.00
10 - FUS	10.00	65.00		3.00	2.00	1.00		81.00
11 - UNISI	10.00	100.00		3.00	2.00	1.00		116.00
12 - Accare	10.00	55.00		3.00	2.00	1.00		71.00
13 - IDIBGI-CERCA	10.00	55.00	10.00	3.00	2.00	1.00		81.00
14 - IMU	10.00	60.00		3.00	2.00	1.00		76.00
Total Person-Months	110.00	393.00	257.00	232.00	78.00	67.00	0.00	1137.00

LIST OF DELIVERABLES

Deliverables

Grant Preparation (Deliverables screen) — Enter the info.

The labels used mean:

Public — fully open (⚠ automatically posted online)
Sensitive — limited under the conditions of the Grant Agreement
EU classified —RESTREINT-UE/EU-RESTRICTED, CONFIDENTIEL-UE/EU-CONFIDENTIAL, SECRET-UE/EU-SECRET under Decision 2015/444

Deliverable No	Deliverable Name	Work Package No	Lead Beneficiary	Type	Dissemination Level	Due Date (month)
D1.1	Documents submitted to competent authorities to initiate the adult and child clinical trials	WP1	1 - EBRIS	R — Document, report	SEN - Sensitive	4
D1.2	eCRF Validation Report, eCRF Release Report	WP1	1 - EBRIS	R — Document, report	SEN - Sensitive	5
D1.3	Mid-term recruitment report (paediatric & adult trials)	WP1	1 - EBRIS	R — Document, report	SEN - Sensitive	30
D1.4	Final recruitment report (paediatric and adult trials)	WP1	1 - EBRIS	R — Document, report	SEN - Sensitive	50
D1.5	Report on the status of posting results	WP1	1 - EBRIS	R — Document, report	SEN - Sensitive	54
D2.1	Report on patient socio-demographic and clinical anamnestic assessment	WP2	11 - UNISI	R — Document, report	SEN - Sensitive	48
D2.2	Report on patient phsycopathological aspects	WP2	11 - UNISI	R — Document, report	SEN - Sensitive	48
D2.3	Report on patient functioning and quality of life	WP2	11 - UNISI	R — Document, report	SEN - Sensitive	48
D2.4	Report on patient resistance to treatment	WP2	11 - UNISI	R — Document, report	SEN - Sensitive	48
D2.5	Report on patient EEG monitoring	WP2	8 - Cephalgo	R — Document, report	SEN - Sensitive	48

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Deliverable No	Deliverable Name	Work Package No	Lead Beneficiary	Type	Dissemination Level	Due Date (month)
D2.6	Global report on non-biological biomarkers	WP2	1 - EBRIS	R — Document, report	SEN - Sensitive	48
D3.1	Report on analysis of inflammatory markers and growth factors	WP3	3 - EURECAT	R — Document, report	SEN - Sensitive	52
D3.2	Report on metabolomic analysis	WP3	3 - EURECAT	R — Document, report	SEN - Sensitive	52
D3.3	Report on analysis of lipoprotein profile	WP3	3 - EURECAT	R — Document, report	SEN - Sensitive	52
D3.4	Report on microbiome analysis	WP3	4 - PERSEUS BIOMICS	R — Document, report	SEN - Sensitive	52
D3.5	Report on transcriptomics analysis	WP3	1 - EBRIS	R — Document, report	SEN - Sensitive	52
D3.6	Report on epigenomic and genomic analysis	WP3	2 - CEINGE	R — Document, report	SEN - Sensitive	52
D3.7	Report on pharmacogenetic and long QT phenotype	WP3	13 - IDIBGI-CERCA	R — Document, report	SEN - Sensitive	52
D3.8	Report on hormonal analysis	WP3	1 - EBRIS	R — Document, report	SEN - Sensitive	52
D3.9	Report on immuno-profiling by MVA	WP3	7 - PROTOBIOS	R — Document, report	SEN - Sensitive	52
D3.10	Report on biological biomarkers	WP3	1 - EBRIS	R — Document, report	SEN - Sensitive	54
D3.11	Final repository of the OPADE biobank	WP3	1 - EBRIS	OTHER	PU - Public	54
D4.1	Final report including set up of the tool and on patient support session	WP4	6 - Mama Health	R — Document, report	SEN - Sensitive	50
D4.2	Report on data integration and validation	WP4	5 - AIE	R — Document, report	SEN - Sensitive	52

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Deliverable No	Deliverable Name	Work Package No	Lead Beneficiary	Type	Dissemination Level	Due Date (month)
D4.3	First version on the AI-powered predictive tool	WP4	5 - AIE	DEM — Demonstrator, pilot, prototype	SEN - Sensitive	30
D4.4	Report on the development of the AI-powered predictive tool	WP4	5 - AIE	R — Document, report	SEN - Sensitive	54
D4.5	Report on the regulatory status of the AI-predictive tool	WP4	5 - AIE	R — Document, report	SEN - Sensitive	54
D5.1	Dissemination, communication & exploitation plan	WP5	9 - BIOKERALTY	R — Document, report	SEN - Sensitive	6
D5.2	Project dedicated public website	WP5	9 - BIOKERALTY	DEC —Websites, patent filings, videos, etc	PU - Public	6
D5.3	Interim dissemination, communication & exploitation plan 1	WP5	9 - BIOKERALTY	R — Document, report	SEN - Sensitive	18
D5.4	Interim dissemination, communication & exploitation plan 2	WP5	9 - BIOKERALTY	R — Document, report	SEN - Sensitive	40
D5.5	Final dissemination, communication & exploitation plan	WP5	9 - BIOKERALTY	R — Document, report	PU - Public	54
D5.6	Clinical guidelines analysis and update	WP5	9 - BIOKERALTY	R — Document, report	PU - Public	54
D5.7	Report on events with stakeholders	WP5	9 - BIOKERALTY	R — Document, report	SEN - Sensitive	54
D5.8	Report on IPR generated over the project and future exploitation strategy	WP5	1 - EBRIS	R — Document, report	SEN - Sensitive	54

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Deliverable No	Deliverable Name	Work Package No	Lead Beneficiary	Type	Dissemination Level	Due Date (month)
D6.1	Project Quality Handbook	WP6	1 - EBRIS	R — Document, report	PU - Public	3
D6.2	Data Management Plan (DMP)	WP6	1 - EBRIS	DMP — Data Management Plan	SEN - Sensitive	6
D7.1	OEI - Requirement No. 1	WP7	1 - EBRIS	ETHICS	SEN - Sensitive	1
D7.2	OEI - Requirement No. 2	WP7	1 - EBRIS	ETHICS	SEN - Sensitive	18
D7.3	OEI - Requirement No. 3	WP7	1 - EBRIS	ETHICS	SEN - Sensitive	36
D7.4	OEI - Requirement No. 4	WP7	1 - EBRIS	ETHICS	SEN - Sensitive	54

Deliverable D1.1 – Documents submitted to competent authorities to initiate the adult and child clinical trials

Deliverable Number	D1.1	**Lead Beneficiary**	1. EBRIS
Deliverable Name	Documents submitted to competent authorities to initiate the adult and child clinical trials		
Type	R — Document, report	**Dissemination Level**	SEN - Sensitive
Due Date (month)	4	**Work Package No**	WP1

Description
The final version of the study protocol as submitted to regulators, wiht the registration number of the CT in a WHO or ICMJE-approved registry and approvals from ethics committees and national competent authorities if applicable, prior to enrolment of first subject in at least one clinical centre.

Deliverable D1.2 – eCRF Validation Report, eCRF Release Report

Deliverable Number	D1.2	**Lead Beneficiary**	1. EBRIS
Deliverable Name	eCRF Validation Report, eCRF Release Report		
Type	R — Document, report	**Dissemination Level**	SEN - Sensitive
Due Date (month)	5	**Work Package No**	WP1

Description
The validation approach establishes that the requirements of the OPADE project are respected from the design stage. It is based on a risk assessment taking into account the intended use of the system and the potential of the system to affect the protection of human subjects and the reliability of clinical trial results.

Deliverable D1.3 – Mid-term recruitment report (paediatric & adult trials)

Deliverable Number	D1.3	**Lead Beneficiary**	1. EBRIS
Deliverable Name	Mid-term recruitment report (paediatric & adult trials)		
Type	R — Document, report	**Dissemination Level**	SEN - Sensitive
Due Date (month)	30	**Work Package No**	WP1

Description
Statistical data on the enrollment process in the different recruitment sites: number of subjects who were included at each site (frequency counts and percentages based on the number of subjects contributing data into the study), subject discontinuations and departures from the study protocol, overview of problems in recruitment and, if applicable, a detailed description of implemented and planned measures to compensate for any incurred delays.

Deliverable D1.4 – Final recruitment report (paediatric and adult trials)

Deliverable Number	D1.4	**Lead Beneficiary**	1. EBRIS
Deliverable Name	Final recruitment report (paediatric and adult trials)		
Type	R — Document, report	**Dissemination Level**	SEN - Sensitive

Due Date (month)	50	Work Package No	WP1

Description
Report on the completeness and accuracy of data collected, on their reliability and adequacy if used as variables in statistical analyses of interest and on the outcomes of the statistical analyses performed

Deliverable D1.5 – Report on the status of posting results

Deliverable Number	D1.5	Lead Beneficiary	1. EBRIS
Deliverable Name	Report on the status of posting results		
Type	R — Document, report	Dissemination Level	SEN - Sensitive
Due Date (month)	54	Work Package No	WP1

Description
Summary results that must be posted in the applicable registry/ies (where the study was registered) even if the timing of posting of results falls outside of the grant period

Deliverable D2.1 – Report on patient socio-demographic and clinical anamnestic assessment

Deliverable Number	D2.1	Lead Beneficiary	11. UNISI
Deliverable Name	Report on patient socio-demographic and clinical anamnestic assessment		
Type	R — Document, report	Dissemination Level	SEN - Sensitive
Due Date (month)	48	Work Package No	WP2

Description
Socio-demographic information and clinical history will be collected with a specific form. Age, gender, ethnic group, education; marital, employment and housing status will be recorded, along with clinical history pertaining to number of acute episodes, number of previous hospitalisations, history of suicide attempts, main and comorbid diagnoses, etc.

Deliverable D2.2 – Report on patient phsycopathological aspects

Deliverable Number	D2.2	Lead Beneficiary	11. UNISI
Deliverable Name	Report on patient phsycopathological aspects		
Type	R — Document, report	Dissemination Level	SEN - Sensitive
Due Date (month)	48	Work Package No	WP2

Description
Psychopathological aspects will be tracked and measured via the Hamilton Rating Scale for Depression (HAM-D), the Beck Depression Inventory, the Montgomery–Åsberg Depression Rating Scale (MADRS) and the Mood Spectrum-Self Report-Current (Mood_SR_C, Mood_SR last month), which is a psychometrically questionnaire evaluating the presence of a wide range of features of mood psychopathology.

Deliverable D2.3 – Report on patient functioning and quality of life

Deliverable Number	D2.3	**Lead Beneficiary**	11. UNISI
Deliverable Name	Report on patient functioning and quality of life		
Type	R — Document, report	**Dissemination Level**	SEN - Sensitive
Due Date (month)	48	**Work Package No**	WP2

Description
A report will be produced on the aspects of quality of life, based on the clinical interviews carried out with the subjects involved, and on the scores obtained on the Short form 36 (adult form) and then Pediatric Quality or Life Inventory (PedsQL) scales. The main indicators of the quality of life of the sample will be analyzed through the presentation of the most common statistical indices (frequency distribution, average scores, etc.)

Deliverable D2.4 – Report on patient resistance to treatment

Deliverable Number	D2.4	**Lead Beneficiary**	11. UNISI
Deliverable Name	Report on patient resistance to treatment		
Type	R — Document, report	**Dissemination Level**	SEN - Sensitive
Due Date (month)	48	**Work Package No**	WP2

Description
A report will be produced on the resistance to treatment of the subjects enrolled, for the current depressive episode, through a pharmacological anamnestic analysis, carried out through the Antidepressant Treatment Record (ATR). The main indicators of resistance to treatment (number of drug trials, duration of illness, etc.) of the sample will be analyzed through the presentation of the most common statistical indices (frequency distribution, average scores, etc.)

Deliverable D2.5 – Report on patient EEG monitoring

Deliverable Number	D2.5	**Lead Beneficiary**	8. Cephalgo
Deliverable Name	Report on patient EEG monitoring		
Type	R — Document, report	**Dissemination Level**	SEN - Sensitive
Due Date (month)	48	**Work Package No**	WP2

Description
Report on the observed brainwave variation across patients of MDD throughout the treatment plan and the corresponding correlations derived by artificial intelligence.

Deliverable D2.6 – Global report on non-biological biomarkers

Deliverable Number	D2.6	**Lead Beneficiary**	1. EBRIS
Deliverable Name	Global report on non-biological biomarkers		
Type	R — Document, report	**Dissemination Level**	SEN - Sensitive
Due Date (month)	48	**Work Package No**	WP2

Description
A collective report resuming highlights from the assessments from socio-demographic, clinical anamnestic, and phsycopathological aspects, patient quality of life, patient resistance, and EEG measurement.

Deliverable D3.1 – Report on analysis of inflammatory markers and growth factors

Deliverable Number	D3.1	**Lead Beneficiary**	3. EURECAT
Deliverable Name	Report on analysis of inflammatory markers and growth factors		
Type	R — Document, report	**Dissemination Level**	SEN - Sensitive
Due Date (month)	52	**Work Package No**	WP3

Description
Proposed inflammatory markers and growth factors will be quantitated using the multiplexed immunoassay technology and a report with the levels of those molecules in response to the treatment will be delivered.

Deliverable D3.2 – Report on metabolomic analysis

Deliverable Number	D3.2	**Lead Beneficiary**	3. EURECAT
Deliverable Name	Report on metabolomic analysis		
Type	R — Document, report	**Dissemination Level**	SEN - Sensitive
Due Date (month)	52	**Work Package No**	WP3

Description
Data obtained from metabolomic analyses (tryptophan metabolism, acylcarnitines and phenolic compounds) will be evaluated to characterize the metabolic profile of patients, providing a complete list of metabolite levels and ratios.

Deliverable D3.3 – Report on analysis of lipoprotein profile

Deliverable Number	D3.3	**Lead Beneficiary**	3. EURECAT
Deliverable Name	Report on analysis of lipoprotein profile		
Type	R — Document, report	**Dissemination Level**	SEN - Sensitive
Due Date (month)	52	**Work Package No**	WP3

Description
Lipoprotein profile, analyzed by NMR, will be evaluated and the levels of several forms of different lipoprotein families will be reported after data analysis.

Deliverable D3.4 – Report on microbiome analysis

Deliverable Number	D3.4	**Lead Beneficiary**	4. PERSEUS BIOMICS
Deliverable Name	Report on microbiome analysis		
Type	R — Document, report	**Dissemination Level**	SEN - Sensitive

Due Date (month)	52	Work Package No	WP3

Description
Longitudinal microbiome analysis of all patients over the treatment course is completed, with data available to the consortium for multidimensional biomarker development. Microbiome biomarker validation is conducted, both by validation of literature biomarkers within the OPADE cohort as well as custom statistical analysis to uncover treatment impact on the microbiome. Internal benchmarking analysis is complete and a critical review of the microbiome analysis within the OPADE

Deliverable D3.5 – Report on transcriptomics analysis

Deliverable Number	D3.5	Lead Beneficiary	1. EBRIS
Deliverable Name	Report on transcriptomics analysis		
Type	R — Document, report	Dissemination Level	SEN - Sensitive
Due Date (month)	52	Work Package No	WP3

Description
The Transcriptomics Analysis Report gives OPADE the ability to analyze and understand if the investigation produces the expected results in the research context through validated biological pathways

Deliverable D3.6 – Report on epigenomic and genomic analysis

Deliverable Number	D3.6	Lead Beneficiary	2. CEINGE
Deliverable Name	Report on epigenomic and genomic analysis		
Type	R — Document, report	Dissemination Level	SEN - Sensitive
Due Date (month)	52	Work Package No	WP3

Description
Raw data obtained by targeted and whole genome DNA methylation analyses from all collected samples. Pre-analyzed methylation data by first level bioinformatic analysis. A list of epigenetic markers identified in group of patients. A list of genetic variants identified for each patient investigated.

Deliverable D3.7 – Report on pharmacogenetic and long QT phenotype

Deliverable Number	D3.7	Lead Beneficiary	13. IDIBGI-CERCA
Deliverable Name	Report on pharmacogenetic and long QT phenotype		
Type	R — Document, report	Dissemination Level	SEN - Sensitive
Due Date (month)	52	Work Package No	WP3

Description
Four types of genetic variability will be considered: Extensive metabolizers (EM), Poor metabolizers (PM), Intermediate metabolizers (IM), Ultrarapid metabolizers (UM). Genes associated with lonq QT syndrome will be identified. Genetic analysis will be conducted through a saliva sample and associated to cardiovascular risk factors, which will be obtained through a blood sample, electrocardiogramme and data extracted from clinical records (BMI, weigh and high);

sociodemographics, clinical and social functioning outcomes (UKU, UFS, Cognitive scales), QoL and lifestyle, which will be self-reported by patients.

Deliverable D3.8 – Report on hormonal analysis

Deliverable Number	D3.8	**Lead Beneficiary**	1. EBRIS
Deliverable Name	Report on hormonal analysis		
Type	R — Document, report	**Dissemination Level**	SEN - Sensitive
Due Date (month)	52	**Work Package No**	WP3

Description
The serum concentration of cortisol in people with MDD is higher than in the unaffected population. An average concentration of around 12 mcg/dL is reported in the literature compared to so-called 'healthy' people (8.0 mcg/dL) (Bertollo et al., 2020). The effectiveness of treatment would be demonstrated by lowering the average cortisol concentration from 12 mcg/dL to more physiological values. The integrated treatment proposed by the OPADE Consortium and the use of AI algorithms would lead to the development of a predictive model of treatment effectiveness

Deliverable D3.9 – Report on immuno-profiling by MVA

Deliverable Number	D3.9	**Lead Beneficiary**	7. PROTOBIOS
Deliverable Name	Report on immuno-profiling by MVA		
Type	R — Document, report	**Dissemination Level**	SEN - Sensitive
Due Date (month)	52	**Work Package No**	WP3

Description
Report on antibody epitope profiling of MDD and related data information that may include also data from the internal review process of other deliverables, drafts of conference presentations and manuscripts, for example.”

Deliverable D3.10 – Report on biological biomarkers

Deliverable Number	D3.10	**Lead Beneficiary**	1. EBRIS
Deliverable Name	Report on biological biomarkers		
Type	R — Document, report	**Dissemination Level**	SEN - Sensitive
Due Date (month)	54	**Work Package No**	WP3

Description
Biological biomarkers report produces unbiased and high depth analysis with high specificity and quantitative precision, correlating the most relevant information coming from high-throughput equipment and amnestic sources

Deliverable D3.11 – Final repository of the OPADE biobank

Deliverable Number	D3.11	**Lead Beneficiary**	1. EBRIS
Deliverable Name	Final repository of the OPADE biobank		

Type	OTHER	Dissemination Level	PU - Public
Due Date (month)	54	Work Package No	WP3

Description
Set up and manage a biobank collecting biospecimens for future research exploring the interplay between multiomics data in relation to the environment. Open to other researchers, subject to approval to an internal committee that will evaluate the scientifically validity of the request.

Deliverable D4.1 – Final report including set up of the tool and on patient support session

Deliverable Number	D4.1	Lead Beneficiary	6. Mama Health
Deliverable Name	Final report including set up of the tool and on patient support session		
Type	R — Document, report	Dissemination Level	SEN - Sensitive
Due Date (month)	50	Work Package No	WP4

Description
Final report of self-reported patient information and analysis of the patient journey as described by patients in the mama health tool. Description of the main events of the patient journey, correlations and root-cause analysis of events across the journey, analysis of the different journey of different subgroups of patients.

Deliverable D4.2 – Report on data integration and validation

Deliverable Number	D4.2	Lead Beneficiary	5. AIE
Deliverable Name	Report on data integration and validation		
Type	R — Document, report	Dissemination Level	SEN - Sensitive
Due Date (month)	52	Work Package No	WP4

Description
The heterogeneous retrospective and prospective structured and unstructured data will be integrated into a cloud Data Lake, enabling versioning, querying, exploration, processing and modelling, following the DataOps best practice.

Deliverable D4.3 – First version on the AI-powered predictive tool

Deliverable Number	D4.3	Lead Beneficiary	5. AIE
Deliverable Name	First version on the AI-powered predictive tool		
Type	DEM — Demonstrator, pilot, prototype	Dissemination Level	SEN - Sensitive
Due Date (month)	30	Work Package No	WP4

Description
We will develop and automate complex pipelines, starting with raw data (clinical & demographical, omics, signals, etc.) preprocessing, transforming into the format required by the AI/ML algorithms, modelling and explaining the prediction with XAI

Deliverable D4.4 – Report on the development of the AI-powered predictive tool

Deliverable Number	D4.4	Lead Beneficiary	5. AIE
Deliverable Name	Report on the development of the AI-powered predictive tool		
Type	R — Document, report	Dissemination Level	SEN - Sensitive
Due Date (month)	54	Work Package No	WP4

Description
We will develop, implement and validate the OPADE predictive tools using the retrospective and prospective patients' data and the AI-powered automated platform

Deliverable D4.5 – Report on the regulatory status of the AI-predictive tool

Deliverable Number	D4.5	Lead Beneficiary	5. AIE
Deliverable Name	Report on the regulatory status of the AI-predictive tool		
Type	R — Document, report	Dissemination Level	SEN - Sensitive
Due Date (month)	54	Work Package No	WP4

Description
To prepare for the commercialization of the OPADE predictive tools in the EU and USA markets, we will establish a regulatory roadmap for EC Mark and FDA approval.

Deliverable D5.1 – Dissemination, communication & exploitation plan

Deliverable Number	D5.1	Lead Beneficiary	9. BIOKERALTY
Deliverable Name	Dissemination, communication & exploitation plan		
Type	R — Document, report	Dissemination Level	SEN - Sensitive
Due Date (month)	6	Work Package No	WP5

Description
Project’s dissemination strategy with its time-plan

Deliverable D5.2 – Project dedicated public website

Deliverable Number	D5.2	Lead Beneficiary	9. BIOKERALTY
Deliverable Name	Project dedicated public website		
Type	DEC —Websites, patent filings, videos, etc	Dissemination Level	PU - Public
Due Date (month)	6	Work Package No	WP5

Description
The website will include the description of the project, the consortium partners, the public results and demonstrators.

The portal will also contain a list of public deliverables from the project, together with relevant related scientific news and open access papers. This portal is linked with the social media tools (e.g. Twitter, Facebook etc.).

Deliverable D5.3 – Interim dissemination, communication & exploitation plan 1

Deliverable Number	D5.3	**Lead Beneficiary**	9. BIOKERALTY
Deliverable Name	Interim dissemination, communication & exploitation plan 1		
Type	R — Document, report	**Dissemination Level**	SEN - Sensitive
Due Date (month)	18	**Work Package No**	WP5

Description
2nd release of the exploitation plan of the project results

Deliverable D5.4 – Interim dissemination, communication & exploitation plan 2

Deliverable Number	D5.4	**Lead Beneficiary**	9. BIOKERALTY
Deliverable Name	Interim dissemination, communication & exploitation plan 2		
Type	R — Document, report	**Dissemination Level**	SEN - Sensitive
Due Date (month)	40	**Work Package No**	WP5

Description
3rd release of the exploitation plan of the project results

Deliverable D5.5 – Final dissemination, communication & exploitation plan

Deliverable Number	D5.5	**Lead Beneficiary**	9. BIOKERALTY
Deliverable Name	Final dissemination, communication & exploitation plan		
Type	R — Document, report	**Dissemination Level**	PU - Public
Due Date (month)	54	**Work Package No**	WP5

Description
Report on the executed exploitation plan and on the achieved goals

Deliverable D5.6 – Clinical guidelines analysis and update

Deliverable Number	D5.6	**Lead Beneficiary**	9. BIOKERALTY
Deliverable Name	Clinical guidelines analysis and update		
Type	R — Document, report	**Dissemination Level**	PU - Public
Due Date (month)	54	**Work Package No**	WP5

Description
Assessment and compilation of exisiting clinical guideliness, proposals and actions for its update based on project results

Deliverable D5.7 – Report on events with stakeholders

Deliverable Number	D5.7	Lead Beneficiary	9. BIOKERALTY
Deliverable Name	Report on events with stakeholders		
Type	R — Document, report	Dissemination Level	SEN - Sensitive
Due Date (month)	54	Work Package No	WP5

Description
Stakeholders databases, recomendations and workshops outputs

Deliverable D5.8 – Report on IPR generated over the project and future exploitation strategy

Deliverable Number	D5.8	Lead Beneficiary	1. EBRIS
Deliverable Name	Report on IPR generated over the project and future exploitation strategy		
Type	R — Document, report	Dissemination Level	SEN - Sensitive
Due Date (month)	54	Work Package No	WP5

Description
Potential intellectual property protection actions and and the exploitation strategies to be implemented

Deliverable D6.1 – Project Quality Handbook

Deliverable Number	D6.1	Lead Beneficiary	1. EBRIS
Deliverable Name	Project Quality Handbook		
Type	R — Document, report	Dissemination Level	PU - Public
Due Date (month)	3	Work Package No	WP6

Description
Quality standards to meet in the managing and implementation of the project in line with guidelines from EU Commission, Grant Agreement and Consortium Agreement

Deliverable D6.2 – Data Management Plan (DMP)

Deliverable Number	D6.2	Lead Beneficiary	1. EBRIS
Deliverable Name	Data Management Plan (DMP)		
Type	DMP — Data Management Plan	Dissemination Level	SEN - Sensitive
Due Date (month)	6	Work Package No	WP6

Description
1st release of the DMP that will be implemented following the open data management guidelines of the Horizon Europe Programme

Deliverable D7.1 – OEI - Requirement No. 1

Deliverable Number	D7.1	Lead Beneficiary	1. EBRIS
Deliverable Name	OEI - Requirement No. 1		
Type	ETHICS	Dissemination Level	SEN - Sensitive
Due Date (month)	1	Work Package No	WP7

Description
While the applicants provided a comprehensive ethics self-assessment, some concerns were not clearly addressed, e.g. incidental findings during EEG measurement; proper handling of vulnerable patients; safety issues for research staff and research participants in countries exposed to political instability. Therefore, an Ethics Advisor must be appointed to monitor the ethics issues involved in the project and how they are handled. A report by the Ethics Advisor must be submitted as a deliverable at the end of each reporting period. Guidance for Ethics Advisors/Boards can be found under: https://ec.europa.eu/info/funding-tenders/opportunities/docs/2021-2027/horizon/guidance/roles-and-functions-of-ethics-advisory-ethics-advisory-boards-in-ec-funded-projects_he_en.pdf.

Deliverable D7.2 – OEI - Requirement No. 2

Deliverable Number	D7.2	Lead Beneficiary	1. EBRIS
Deliverable Name	OEI - Requirement No. 2		
Type	ETHICS	Dissemination Level	SEN - Sensitive
Due Date (month)	18	Work Package No	WP7

Description
1st report of the ethics advisor.

Deliverable D7.3 – OEI - Requirement No. 3

Deliverable Number	D7.3	Lead Beneficiary	1. EBRIS
Deliverable Name	OEI - Requirement No. 3		
Type	ETHICS	Dissemination Level	SEN - Sensitive
Due Date (month)	36	Work Package No	WP7

Description
2nd report of the ethics advisor.

Deliverable D7.4 – OEI - Requirement No. 4

Deliverable Number	D7.4	Lead Beneficiary	1. EBRIS
Deliverable Name	OEI - Requirement No. 4		
Type	ETHICS	Dissemination Level	SEN - Sensitive
Due Date (month)	54	Work Package No	WP7

Description
3rd report of the ethics advisor.

LIST OF MILESTONES

Milestones

Grant Preparation (Milestones screen) — Enter the info.

Milestone No	Milestone Name	Work Package No	Lead Beneficiary	Means of Verification	Due Date (month)
1	First patient includes in the study (teen or young adult)	WP1	1-EBRIS	Report of the visit established by the clinical centre.	7
2	First group of patients integrated in the empowerment digital tool	WP4	6-Mama Health	MMH interim research report	8
3	First selection of the key biomarkers is done (80%)	WP3	5-AIE	Research report on informative biomarkers selection established by AIE	18
4	First AI-powered patient pattern is presented to the consortium (v1.0)	WP3	5-AIE	Research report on relevant patterns discovered by AI, established by AIE	30
5	350th patient completed the study	WP1	1-EBRIS	Report of the visit established by all the clinical centre	48
6	24-month follow-up on brainwaves performed on 350 patients	WP2	8-Cephalgo	Report established by CEP	48
7	4 time points for the key biomarkers are done for 350 patients	WP3	1-EBRIS	Report on the biological biomarker compiled by EBRIS	52
8	1 new clinical guideline is available to be circulated outside of the consortium	WP5	9-BIOKERALTY	Draft document circulated to consortium	51
9	v2.0 OPADE AI-predictive tool is ready to be deployed in clinical practice following appropriate certification	WP3	5-AIE	Advancement report on the discovered AI predictive tools, established by AIE	52
10	Mid-term Ethics audit	WP7	1-EBRIS	A medium-term ethical audit to identify and correctly address any ethical problem that may have been arisen during the project	30

LIST OF CRITICAL RISKS

Critical risks & risk management strategy

Grant Preparation (Critical Risks screen) — Enter the info.

Risk number	Description	Work Package No(s)	Proposed Mitigation Measures
1	Too many patients drop the study before the end of the commitment period	WP4, WP5, WP2, WP3, WP6, WP1	The challenge of the study design resides within the length of the study which is in fact key to conclude on all the pre-defined objectives.The tool of MMH that ensure patient empowerment will boost patient adherence to clinical study through regular and unformal meetings. This is a key tool in such a clinical design.
2	Clinical trial is not complete because of slow recruitment, patient shortage, lack of resources	WP5, WP1	We appointed 10 clinical centres over 5 different countries with a high rate of MDD cases on a regular basis. In particular, the UNISA, is an internal consortium of 6 clinical centres over Italy. Clinical centres committed in their ability to recruit a certain number of patients based on their monthly rate. If the recruitment is too slow, we will envisage to add new clinical centres, following discussion with the PO and the EC.
3	A research or industrial partner leave the consortium	WP4, WP5, WP2, WP3, WP6, WP1	The consortium was built to ensure that the most of the partners are ‘backed-up’ by other partners. Thus, while a partner may exist, the immediate activities can be taken over by another partner to prevent project hold. The consortium will discuss with the PO project officer to rebalance the budget and finally bring another partner to support the work.
4	Delay in regulatory approval for the clinical trials	WP4, WP2, WP3, WP1	In our planning, we dedicated 4 months at the beginning of the project to obtain he green lights from the EMA and IRBs to initiate the clinical trials enrolled in the project. The clinical activities are led by EBRIS. No new drugs are tested on these clinical trials that generally ease approval from the competent authorities. Paediatric trial: A specific clinical trial will be led on teenagers. We will define the PIP (paediatric investigation plans) at the beginning of the project. The approval for FUS (Colombian site) is supported by BIOK (Spanish affiliated entity), who is experienced with the local mechanisms. FUS has currently 30 ongoing clinical trials, including one in depressive disorders (bipolarity) with a cohort of more than 6800 MDD patients and will thus easily obtain the approval from the local authority.
5	Biomarker correlation is not conclusive to optimise anti-depressant efficacy for MDD patients	WP4, WP5, WP2	We will include a significant number of patients on the study (350) to ensure statistical differences. The decision of testing particular biomarkers relies on established clinical proof-of-concept that are documented in the literature and OPADE clinical centres own practices. We are testing a large variety of biomarkers. We will run different correlations if needed, excluding certain types of biomarkers. Results and analysis will be performed in order to

Critical risks & risk management strategy

Grant Preparation (Critical Risks screen) — Enter the info.

Risk number	Description	Work Package No(s)	Proposed Mitigation Measures
			be managed separately. Samples will be kept in EBRIS facilities to run further analysis if needed.
6	The identify set up of biomarkers is too expansive to ensure a rapid clinical adoption	WP2, WP3	Multi-omic analysis can become particularly expensive that will limit the clinical adoption of our potential findings. Through the unbiaised analysis strategy and subsequent selection of the biomkarers of interest determined, we will always consider the costs of the analysis. At equivalent results, the less expensive biomarkers will be chosen and integrate in our AI-predicitve model.
7	Data sharing between the partners	WP4, WP5, WP2, WP3, WP6, WP1	Data sharing will be regulated by the consortium agreement and a specific Data Management Plan will be put in place as Deliverable at M6. During proposal writing, the different partners discussed of the types of data that will be shared to ensure the power of the AI-predicitve tool and the type of data that will remain the sole property of the leading partner. Commercial modalities will be discussed at a more advanced stage of the project.
8	Batch effect due to the sample collection from different centres and countries	WP4, WP3	Batch effect will be mitigated during analysis by using two different approaches: 1) quality controls (pool of samples) analyzed repeteadly during the analysis of all samples; 2) use of specific internal standards (labeled standards) to correct signal drift and possible differences during metabolite extraction.
9	Ethical concern for EEG monitoring	WP2, WP7	The patients might feel being violated as their emotions are interpreted by AI - in this case, one should verify if the patients want to share their brainwaves and the corresponding as a part of feedback about the treatment. For those who don't want to, they won't be the considered ones in this study. The patients might misunderstand that our AI can read their mind - our AI can only analyze the patients' emotions, positive or negative, active or not active. This risk can be mitigated by clear instruction and introduction about our EEG monitoring system. The patients might worry the predicted emotions are biased, for example more accurate for men than women - to avoid such a problem, we implement the reference period that no analysis will be given but just collecting patients' emotion feedback. With the patients' emotion feedback and the general interpretation of brainwave-based emotions, we start to provide the emotion analysis to the clinicians to avoid the biased emotion analysis and to ensure the accuracy to individual patients.