Call: HORIZON-HLTH-2022-TOOL-11

(Tools and technologies for a healthy society (Single Stage - 2022))

Topic: HORIZON-HLTH-2022-TOOL-11-01

Type of Action: HORIZON-RIA

Proposal number: 101095436

Proposal acronym: OPADE

Type of Model Grant Agreement: HORIZON Action Grant Budget-Based

Table of contents

Proposal ID **101095436**

Acronym **OPADE**

1 - General information

Fields marked * are mandatory to fill.

Topic	HORIZON-HLTH-2022-TOOL-11-01	Type of Action	HORIZON-RIA
Call	HORIZON-HLTH-2022-TOOL-11	Type of Model Grant Agreement	HORIZON-AG

Acronym: OPADE

Proposal title: Optimise and predict antidepressant efficacy for patient with major depressive disorders using multi-omics analysis and AI-predictive tool

Note that for technical reasons, the following characters are not accepted in the Proposal Title and will be removed: < > " &

Duration in months: 54

Fixed keyword 1: Biochemistry and molecular biology

Fixed keyword 2: Other clinical medicine subjects

Free keywords: *Major depression disorder, AI-predictive tool, anti-depressant efficacy, gut-brain-axis*

Abstract *

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.

Remaining characters 7

Has this proposal (or a very similar one) been submitted in the past 2 years in response to a call for proposals under any EU programme, including the current call? ○ Yes ◉ No

Please give the proposal reference or contract number.

Administrative forms

Proposal ID **101095436**

Acronym **OPADE**

Declarations

Field(s) marked * are mandatory to fill.

1) We declare to have the explicit consent of all applicants on their participation and on the content of this proposal. *	☒
2) We confirm that the information contained in this proposal is correct and complete and that none of the project activities have started before the proposal was submitted (unless explicitly authorised in the call conditions).	☒
3) We declare: - to be fully compliant with the eligibility criteria set out in the call - not to be subject to any exclusion grounds under the EU Financial Regulation 2018/1046 - to have the financial and operational capacity to carry out the proposed project.	☒
4) We acknowledge that all communication will be made through the Funding & Tenders Portal electronic exchange system and that access and use of this system is subject to the Funding & Tenders Portal Terms and Conditions.	☒
5) We have read, understood and accepted the Funding & Tenders Portal Terms & Conditions and Privacy Statement that set out the conditions of use of the Portal and the scope, purposes, retention periods, etc. for the processing of personal data of all data subjects whose data we communicate for the purpose of the application, evaluation, award and subsequent management of our grant, prizes and contracts (including financial transactions and audits).	☒
6) We declare that the proposal complies with ethical principles (including the highest standards of research integrity as set out in the ALLEA European Code of Conduct for Research Integrity, as well as applicable international and national law, including the Charter of Fundamental Rights of the European Union and the European Convention on Human Rights and its Supplementary Protocols. Appropriate procedures, policies and structures are in place to foster responsible research practices, to prevent questionable research practices and research misconduct, and to handle allegations of breaches of the principles and standards in the Code of Conduct.	☒
7) We declare that the proposal has an exclusive focus on civil applications (activities intended to be used in military application or aiming to serve military purposes cannot be funded). If the project involves dual-use items in the sense of Regulation 2021/821, or other items for which authorisation is required, we confirm that we will comply with the applicable regulatory framework (e.g. obtain export/import licences before these items are used).	☒
8) We confirm that the activities proposed do not - aim at human cloning for reproductive purposes; - intend to modify the genetic heritage of human beings which could make such changes heritable (with the exception of research relating to cancer treatment of the gonads, which may be financed), or - intend to create human embryos solely for the purpose of research or for the purpose of stem cell procurement, including by means of somatic cell nuclear transfer. - lead to the destruction of human embryos (for example, for obtaining stem cells) These activities are excluded from funding.	☒
9) We confirm that for activities carried out outside the Union, the same activities would have been allowed in at least one EU Member State.	☒

The coordinator is only responsible for the information relating to their own organisation. Each applicant remains responsible for the information declared for their organisation. If the proposal is retained for EU funding, they will all be required to sign a declaration of honour.

False statements or incorrect information may lead to administrative sanctions under the EU Financial Regulation.

2 - Participants

List of participating organisations

#	Participating Organisation Legal Name	Country	Role	Action
1	FONDAZIONE EBRIS	IT	Coordinator	
2	CEINGE BIOTECNOLOGIE AVANZATE SCARL	IT	Partner	
3	FUNDACIO EURECAT	ES	Partner	
4	PERSEUS BIOMICS	BE	Partner	
5	ARTIFICIAL INTELLIGENCE EXPERT SRL	RO	Partner	
6	mama health technologies GmbH	DE	Partner	
7	PROTOBIOS OU	EE	Partner	
8	Cephalgo	FR	Partner	
9	BIOKERALTY RESEARCH INSTITUTE AIE	ES	Partner	
10	Fundación Universitaria Sanitas	CO	Partner	
11	UNIVERSITA DEGLI STUDI DI SIENA	IT	Partner	
12	STICHTING UNIVERSITAIRE EN ALGEMENE KINDER - EN JEU	NL	Partner	
13	FUNDACIO INSTITUT D'INVESTIGACIO BIOMEDICA DE GIR(	ES	Partner	
14	ISTANBUL MEDIPOL UNIVERSITESI	TR	Partner	

Organisation data

PIC	Legal name
935386230	*FONDAZIONE EBRIS*

Short name: EUROPEAN BIOMEDICAL RESEARCH INSTITUTE OD SALERNO

Address

Street	VIA DE RENZI 1
Town	SALERNO
Postcode	84125
Country	Italy
Webpage	www.ebris.eu

Specific Legal Statuses

Legal person	yes
Public body	no
Non-profit	yes
International organisation	no
Secondary or Higher education establishment	no
Research organisation	yes

SME Data

Based on the below details from the Participant Registry the organisation is not an SME (small- and medium-sized enterprise) for the call.

SME self-declared status	07/10/2014 - no
SME self-assessment	unknown
SME validation	unknown

Departments carrying out the proposed work

Department 1

Department name: EBRIS ☐ not applicable

☒ Same as proposing organisation's address

Street: VIA DE RENZI 1

Town: SALERNO

Postcode: 84125

Country: Italy

Links with other participants

Type of link	Participant

Main contact person

This will be the person the EU services will contact concerning this proposal (e.g. for additional information, invitation to hearings, sending of evaluation results, convocation to start grant preparation). The data in blue is read-only. Details (name, first name and e-mail) of Main Contact persons should be edited in the step "Participants" of the submission wizard.

Title Prof.

Gender ◯ Woman ◉ Man ◯ Non Binary

First name* **Alessio**

Last name* **Fasano**

E-Mail* **a.fasano@ebris.eu**

Position in org. Scientific Director

Department FONDAZIONE EBRIS ☒ Same as organisation name

☒ Same as proposing organisation's address

Street VIA DE RENZI 1

Town SALERNO Post code 84125

Country Italy

Website *Please enter website*

Phone *+xxx xxxxxxxxx* *Phone 2* *+xxx xxxxxxxxx*

Other contact persons

First Name	Last Name	E-mail	Phone
ECAS	Validation	validation.ecas@gmail.com	+xxx xxxxxxxxx

Researchers involved in the proposal

Title	First Name	Last Name	Gender	Nationality	E-mail	Career Stage	Role of researcher (in the project)	Reference Identifier	Type of identifier
Prof	Alessio	Fasano	Man	United States	a.fasano@ebris.eu	Category A Top grade re	Leading	0000-0002-2134-0261	Orcid ID
Dr	Simone	Di Micco	Man	Italy	s.dimicco@ebris.eu	Category C Recognised	Team member	0000-0002-4688-1080	Orcid ID
Dr	Carmina	Ingenito	Woman	Italy	c.ingenito@ebris.eu	Category C Recognised	Team member	0000-0001-8849-0355	Orcid ID
Dr	Simona	Musella	Woman	Italy	s.musella@ebris.eu	Category C Recognised	Team member	0000-0001-8312-4241	Orcid ID
Dr	Titti	Terracciano	Woman	Italy	t.terracciano@ebris.eu	Category C Recognised	Team member	0000-0001-8306-0989	Orcid ID
Dr	Giorgia	Venutolo	Woman	Italy	g.venutolo@ebris.eu	Category C Recognised	Team member	0000-0001-8396-9412	Orcid ID

Role of participating organisation in the project

Project management	☒
Communication, dissemination and engagement	☐
Provision of research and technology infrastructure	☐
Co-definition of research and market needs	☐
Civil society representative	☐
Policy maker or regulator, incl. standardisation body	☐
Research performer	☒
Technology developer	☐
Testing/validation of approaches and ideas	☐
Prototyping and demonstration	☐
IPR management incl. technology transfer	☐
Public procurer of results	☐
Private buyer of results	☐
Finance provider (public or private)	☐
Education and training	☒
Contributions from the social sciences or/and the humanities	☐
Other If yes, please specify: (Maximum number of characters allowed: 50)	☒

Will be the coordinating Center of the application

List of up to 5 publications, widely-used datasets, software, goods, services, or any other achievements relevant to the call content.

Type of achievement	Short description (Max 500 characters)
Publication	*Di Micco S, Musella S, Scala MC, Sala M, Campiglia P, Bifulco G, Fasano A. In silico Analysis Revealed Potential Anti-SARS-CoV-2 Main Protease Activity by the Zonulin Inhibitor Larazotide Acetate. Front Chem. 2021 Jan 15;8:628609. doi: 10.3389/fchem.2020.628609. eCollection 2020.PMID: 33520943*
Publication	*Yonker LM, Neilan AM, Bartsch Y, Patel AB, Regan J, Arya P, Gootkind E, Park G, Hardcastle M, St John A, Appleman L, Chiu ML, Fialkowski A, De la Flor D, Lima R, Bordt EA, Yockey LJ, D'Avino P, Fischinger S, Shui JE, Lerou PH, Bonventre JV, Yu XG, Ryan ET, Bassett IV, Irimia D, Edlow AG, Alter G, Li JZ, Fasano A. Pediatric Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): Clinical Presentation, Infectivity, and Immune Responses.*
Publication	*Bartsch YC, Wang C, Zohar T, Fischinger S, Atyeo C, Burke JS, Kang J, Edlow AG, Fasano A, Baden LR, Nilles EJ, Woolley AE, Karlson EW, Hopke AR, Irimia D, Fischer ES, Ryan ET, Charles RC, Julg BD, Lauffenburger DA, Yonker LM, Alter G. Humoral signatures of protective and pathological SARS-CoV-2 infection in children.. Nat Med. 2021 Mar;27(3):454-462. doi: 10.1038/s41591-021-01263-3. Epub 2021 Feb 12.PMID: 33589825*
Publication	*Porritt RA, Paschold L, Noval Rivas M, Cheng MH, Yonker LM, Chandnani H, Lopez M, Simnica D, Schultheiß C, Santiskulvong C, van Eyk J, McCormick JK, Fasano A, Bahar I, Binder M, Arditi M. HLA class I-associated expansion of TRBV11-2 T cells in Multisystem Inflammatory Syndrome in Children. J Clin Invest. 2021 Mar 11:146614. doi: 10.1172/JCI146614. Online ahead of print.PMID: 33705359*
Publication	*Gray KJ, Bordt EA, Atyeo C, Deriso E, Akinwunmi B, Young N, Medina Baez A, Shook LL, Cvrk D, James K, De Guzman R, Brigida S, Diouf K, Goldfarb I, Bebell LM, Yonker LM, Fasano A, Rabi SA, Elovitz MA, Alter G, Edlow AG. COVID-19 vaccine response in pregnant and lactating women: a cohort study. Am J Obstet Gynecol. 2021 Mar 24:S0002-9378(21)00187-3. doi: 10.1016/j.ajog.2021.03.023. Online ahead of print.PMID: 33775692*

List of up to 5 most relevant previous projects or activities, connected to the subject of this proposal.

Name of Project or Activity	Short description (Max 500 characters)
GEMMA	*Genome, Environment, Microbiome & Metabolome in Autism: an integrated multi-omic systems biology approach to identify biomarkers for personalized treatment and primary prevention of Autism Spectrum Project ID: 825033 www.gemma-project.eu*
CD-GEMM	*Celiac Disease Microbiome and Metabolomic Study: https://www.massgeneral.org/children/celiac-disease/genomic-environmental-microbiome-and-metabolomic-study/*
IHCMA	*International Human Microbiome Coordination and Support Action. Standardizing clinical metadata Project ID: 964590*

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work.

Name of infrastructure of equipment	Short description (Max 300 characters)
EBRIS	*EBRIS is located in the ex Convento S. Nicola in Salerno and occupies a four story building covering a total of ~12,000 m2 of laboratory, office, and meeting space. There are four large laboratories that can accommodate up to 120 researchers.*

Gender Equality Plan

Does the organization have a Gender Equality Plan (GEP) covering the elements listed below? (•) Yes ( ) No

Minimum process-related requirements (building blocks) for a GEP

- **Publication:** formal document published on the institution's website and signed by the top management
- **Dedicated resources:** commitment of human resources and gender expertise to implement it.
- **Data collection and monitoring:** sex/gender disaggregated data on personnel (and students for establishments concerned) and annual reporting based on indicators.
- **Training:** Awareness raising/trainings on gender equality and unconscious gender biases for staff and decision-makers.
- **Content-wise, recommended areas** to be **covered** and addressed via concrete measures and targets are:
    - work-life balance and organisational culture;
    - gender balance in leadership and decision-making;
    - gender equality in recruitment and career progression;
    - integration of the gender dimension into research and teaching content;
    - measures against gender-based violence including sexual harassment.

PIC	Legal name
999951564	*CEINGE BIOTECNOLOGIE AVANZATE SCARL*

Short name: CEINGE BIOTECNOLOGIE AVANZATE SCARL

Address

Street	VIA GAETANO SALVATORE 486
Town	NAPOLI
Postcode	80145
Country	Italy
Webpage	www.ceinge.unina.it

Specific Legal Statuses

Legal person	yes
Public body	no
Non-profit	yes
International organisation	no
Secondary or Higher education establishment	no
Research organisation	yes

SME Data

Based on the below details from the Participant Registry the organisation is not an SME (small- and medium-sized enterprise) for the call.

SME self-declared status	24/04/1984 - no
SME self-assessment	unknown
SME validation	unknown

Departments carrying out the proposed work

Department 1

Department name	CEINGE Epigenetic Lab	☐ not applicable
	☒ Same as proposing organisation's address	
Street	VIA GAETANO SALVATORE 486	
Town	NAPOLI	
Postcode	80145	
Country	Italy	

Links with other participants

Type of link	Participant

Main contact person

This will be the person the EU services will contact concerning this proposal (e.g. for additional information, invitation to hearings, sending of evaluation results, convocation to start grant preparation). The data in blue is read-only. Details (name, first name and e-mail) of Main Contact persons should be edited in the step "Participants" of the submission wizard.

Title Prof.

Gender ◯ Woman ◉ Man ◯ Non Binary

First name* **Lorenzo**

Last name* **Chiariotti**

E-Mail* **chiariot@unina.it**

Position in org. Leading – Top Researcher - Full Professor

Department CEINGE Epigenetic Lab

☐ Same as organisation name

☒ Same as proposing organisation's address

Street VIA GAETANO SALVATORE 486

Town NAPOLI

Post code 80145

Country Italy

Website *Please enter website*

Phone *+xxx xxxxxxxxx*

Phone 2 *+xxx xxxxxxxxx*

Other contact persons

First Name	Last Name	E-mail	Phone
Marco	Matarese	matarese@ceinge.unina.it	+xxx xxxxxxxxx
Lorenzo	Chiarotti	chiariotti@ceinge.unina.it	+xxx xxxxxxxxx

Researchers involved in the proposal

Title	First Name	Last Name	Gender	Nationality	E-mail	Career Stage	Role of researcher (in the project)	Reference Identifier	Type of identifier
Prof	Lorenzo	Chiariotti	Man	Italy	chiariot@unina.it	Category A Top grade re	Leading	0000-0001-6097-4171	Orcid ID
Prof	Francesca	Lembo	Woman	Italy	francesca.lembo@unina.it	Category B Senior resea	Team member	0000-0002-9697-3952	Orcid ID
Dr	Roberta	Visconti	Woman	Italy	visconti@unina.it	Category B Senior resea	Team member	0000-0001-7613-3801	Orcid ID
Dr	Mariella	Cuomo	Woman	Italy	mariella.cuomo@unina.it	Category C Recognised	Team member	0000-0001-8393-165X	Orcid ID
Dr	Lorena	Coretti	Woman	Italy	lorena.coretti@unina.it	Category C Recognised	Team member	0000-0002-1289-7842	Orcid ID
Dr	Rosa	Della Monica	Woman	Italy	dellamonica@ceinge.unina.it	Category D First stage r	Team member	0000-0002-5933-5556	Orcid ID
Dr	Davide	Costabile	Man	Italy	costabile@ceinge.unina.it	Category D First stage r	Team member	0000-0002-8987-1325	Orcid ID
Dr	Michela	Buonaiuto	Woman	Italy	buonaiutom@ceinge.unina.it	Category D First stage r	Team member	0000-0003-3898-7114	Orcid ID
Dr	Teodolinda	Di Risi	Woman	Italy	dirisi@ceinge.unina.it	Category D First stage r	Team member	0000-0002-8091-3066	Orcid ID
Dr	Marco	Matarese	Man	Italy	matarese@ceinge.unina.it		Team member		

Role of participating organisation in the project

Project management	☐
Communication, dissemination and engagement	☐
Provision of research and technology infrastructure	☒
Co-definition of research and market needs	☐
Civil society representative	☐
Policy maker or regulator, incl. standardisation body	☐
Research performer	☒
Technology developer	☐
Testing/validation of approaches and ideas	☒
Prototyping and demonstration	☒
IPR management incl. technology transfer	☐
Public procurer of results	☐
Private buyer of results	☐
Finance provider (public or private)	☐
Education and training	☒
Contributions from the social sciences or/and the humanities	☐
Other If yes, please specify: (Maximum number of characters allowed: 50)	☐

List of up to 5 publications, widely-used datasets, software, goods, services, or any other achievements relevant to the call content.

Type of achievement	Short description (Max 500 characters)
Publication	*Cuomo M, Keller S, Punzo D, Nuzzo T, Affinito O, Coretti L, Carella M, de Rosa V, Florio E, Boscia F, Avvedimento VE, Cocozza S, Errico F, Usiello A, Chiariotti L. Selective demethylation of two CpG sites causes postnatal activation of the Dao gene and consequent removal of D-serine within the mouse cerebellum. Clin Epigenetics, 11:149, 2019* *doi: 10.1186/s13148-019-0732-z*
Publication	*Keller S, Punzo D, Cuomo M, Affinito O, Coretti L, Sacchi S, Florio E, Lembo F, Carella M, Copetti M, Cocozza S, Balu DT, Errico F, Usiello A, Chiariotti L. DNA methylation landscape of the genes regulating D-serine and D-aspartate metabolism in post-mortem brain from controls and subjects with schizophrenia. Sci Rep, 8:10163, 2018* *doi: 10.1038/s41598-018-28332-x*
Publication	*Keller S, Errico F, Zarrilli F, Florio E, Punzo D, Mansueto S, Angrisano T, Pero R, Lembo F, Castaldo G, Usiello A, Chiariotti L. DNA methylation state of BDNF gene is not altered in prefrontal cortex and striatum of schizophrenia subjects. Psychiatry Res, 220:1147-50, 2014* *doi: 10.1016/j.psychres.2014.08.022*
Publication	*Keller S, Sarchiapone M, Zarrilli F, Videtic A, Ferraro A, Carli V, Sacchetti S, Lembo F, Angiolillo A, Jovanovic N, Pisanti F, Tomaiuolo R, Monticelli A, Balazic J, Roy A, Marusic A, Cocozza S, Fusco A, Bruni CB, Castaldo G, Chiariotti L.* *Increased BDNF promoter methylation in the Wernicke area of suicide subjects. Arch Gen Psychiatry, (JAMA psychiatry) 67:258-67, 2010* *doi: 10.1001/archgenpsychiatry.2010.9*
Publication	*Perillo B, Ombra MN, Bertoni A, Cuozzo C, Sacchetti S, Sasso A, Chiariotti L, Malorni A, Abbondanza C, Avvedimento EV. DNA oxidation as triggered by H3K9me2 demethylation drives estrogen-induced gene expression. Science. 2008 Jan 11;319(5860):202-6. doi: 10.1126/ science.1147674.*

List of up to 5 most relevant previous projects or activities, connected to the subject of this proposal.

Name of Project or Activity	Short description (Max 500 characters)
Epigen Joint Project	*Title: Epigenomic profiling of thyroid cancer* *Funded by: National Council of Research of Italy* *Years: 2013-2018 - CNR SP.6.6, EPIGEN Project* *Euro 475.000*
NARSAD *Young Investigator Grant*	*Title: Epigenetic landscape of D-aminoacids system genes during development and in schizophrenia* *Funded by: Brain & Behaviour Research Foundation* *Year: 2017-2019* *70.000 USD*
Epigen Flagship Project	*Title:"Ultra-deep dynamic view of epigenetic modifications in specific genomic territories". Neuroepigenetics research CNR SP.6.6, EPIGEN Project* *Funded by: National Council of Research of Italy* *Euro 300.000*

PRIN	*Title: Epigenetics of neuropsychiatric disorders: DNA methylation in depression and suicidal behaviour. Two-Years.* *Funded by: Italian Ministry of University and Reserach*

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work.

Name of infrastructure of equipment	**Short description (Max 300 characters)**
iScan System	*The iScan System supports the complete portfolio of innovative Illumina assays for genotyping, copy number variation (CNV) analysis, and DNA methylation*
NextSeq550	*Next-generation sequencing system. Relevant characteristics:* *- High-output flow cell* *- Up to 400M single reads* *- Up to 800M paired-end reads*
MiSeq	*Next-generation sequencing system. Relevant characteristics:* *- Read length: 2 × 250 bp* *- Output: 7.5-8.5 Gb* *- Paired-end reads: 24-30M*
PromethION Nanopore system	*Third-generation sequencing system. Relevant characteristics:* *- Read length: up to 50kb* *- Output: terabases of data* *- Theoretical max output: 72 hours at 420 bases / second*

Gender Equality Plan

Does the organization have a Gender Equality Plan (GEP) covering the elements listed below? (•) Yes ( ) No

Minimum process-related requirements (building blocks) for a GEP

- **Publication:** formal document published on the institution's website and signed by the top management
- **Dedicated resources:** commitment of human resources and gender expertise to implement it.
- **Data collection and monitoring:** sex/gender disaggregated data on personnel (and students for establishments concerned) and annual reporting based on indicators.
- **Training:** Awareness raising/trainings on gender equality and unconscious gender biases for staff and decision-makers.
- **Content-wise, recommended areas** to be **covered** and addressed via concrete measures and targets are:
    - work-life balance and organisational culture;
    - gender balance in leadership and decision-making;
    - gender equality in recruitment and career progression;
    - integration of the gender dimension into research and teaching content;
    - measures against gender-based violence including sexual harassment.

PIC	Legal name
928030235	*FUNDACIO EURECAT*

Short name: EURECAT

Address

Street	AVENIDA UNIVERSITAT AUTONOMA 23
Town	CERDANYOLA DEL VALLES (BARCELONA)
Postcode	08290
Country	Spain
Webpage	www.eurecat.org/

Specific Legal Statuses

Legal person	yes
Public body	no
Non-profit	yes
International organisation	no
Secondary or Higher education establishment	no
Research organisation	yes

SME Data

Based on the below details from the Participant Registry the organisation is not an SME (small- and medium-sized enterprise) for the call.

SME self-declared status	04/05/2015 - no
SME self-assessment	unknown
SME validation	unknown

Departments carrying out the proposed work

Department 1

Department name	The Center for Omic Sciences (COS)	☐ not applicable
	☐ Same as proposing organisation's address	
Street	Av. de la Universitat, 1	
Town	Reus, Tarragona	
Postcode	43204	
Country	Spain	

Links with other participants

Type of link	Participant

Main contact person

This will be the person the EU services will contact concerning this proposal (e.g. for additional information, invitation to hearings, sending of evaluation results, convocation to start grant preparation). The data in blue is read-only. Details (name, first name and e-mail) of Main Contact persons should be edited in the step "Participants" of the submission wizard.

Title Dr

Gender (•) Woman ( ) Man ( ) Non Binary

First name* **Nuria**

Last name* **Canela**

E-Mail* **nuria.canela@eurecat.org**

Position in org. Omics Science Technology Unit Director

Department The Center for Omic Sciences (COS)

☐ Same as organisation name

☐ Same as proposing organisation's address

Street Av. de la Universitat, 1

Town Reus, Tarragona

Post code 43204

Country Spain

Website *Please enter website*

Phone *+xxx xxxxxxxxx*

Phone 2 *+xxx xxxxxxxxx*

Other contact persons

First Name	Last Name	E-mail	Phone
Chiara	Baudracco	chiara.baudracco@eurecat.org	+xxx xxxxxxxxx
Alba	Garcia Delgado	alba.garcia@eurecat.org	+xxx xxxxxxxxx

Researchers involved in the proposal

Title	First Name	Last Name	Gender	Nationality	E-mail	Career Stage	Role of researcher (in the project)	Reference Identifier	Type of identifier
Dr	Nuria	Canela	Woman	Spain	nuria.canela@eurecat.org	Category A Top grade re	Leading	0000-0003-0261-2396	Orcid ID
Dr	Salvador	Fernández Arroyo	Man	Spain	salvador.fernandez@eurecat.org	Category B Senior resea	Team member	0000-0003-0147-1712	Orcid ID
Dr	Miguel Angel	Rodríguez Gómez	Man	Spain	miguelangel.rodriguez@eurecat.org	Category B Senior resea	Team member	0000-0001-9568-9821	Orcid ID
Ms	Chiara	Baudracco	Woman	Italy	chiara.baudracco@eurecat.org		Team member		
Mr	Fernando	Porcel	Man	Spain	fernando.porcel@eurecat.org		Team member		

Role of participating organisation in the project

Project management	☐
Communication, dissemination and engagement	☐
Provision of research and technology infrastructure	☐
Co-definition of research and market needs	☐
Civil society representative	☐
Policy maker or regulator, incl. standardisation body	☐
Research performer	☒
Technology developer	☐
Testing/validation of approaches and ideas	☐
Prototyping and demonstration	☐
IPR management incl. technology transfer	☐
Public procurer of results	☐
Private buyer of results	☐
Finance provider (public or private)	☐
Education and training	☐
Contributions from the social sciences or/and the humanities	☐
Other If yes, please specify: (Maximum number of characters allowed: 50)	☐

List of up to 5 publications, widely-used datasets, software, goods, services, or any other achievements relevant to the call content.

Type of achievement	Short description (Max 500 characters)
Publication	*Castañé, H., Baiges-Gaya, G., Hernández-Aguilera, A., Rodríguez-Tomàs, E., Fernández-Arroyo, S., Herrero, P., ... & Joven, J. (2021). Coupling Machine Learning and Lipidomics as a Tool to Investigate Metabolic Dysfunction-Associated Fatty Liver Disease. A General Overview. Biomolecules, 11(3), 473. DOI: 10.3390/biom11030473*
Publication	*Paton, B., Suarez, M., Herrero, P., & Canela, N. (2021). Glycosylation biomarkers associated with age-related diseases and current methods for glycan analysis. International Journal of Molecular Sciences, 22(11), 5788. DOI: 10.3390/ijms22115788*
Publication	*Cabré, N., Luciano-Mateo, F., Baiges-Gayà, G., Fernández-Arroyo, S., Rodríguez-Tomàs, E., Hernández-Aguilera, A., ... & Joven, J. (2020). Plasma metabolic alterations in patients with severe obesity and non-alcoholic steatohepatitis. Alimentary Pharmacology & Therapeutics, 51(3), 374-387. DOI: 10.1111/apt.15606*
Publication	*Samino, S., Vinaixa, M., Díaz, M., Beltran, A., Rodríguez, M. A., Mallol, R., ... & Yanes, O. (2015). Metabolomics reveals impaired maturation of HDL particles in adolescents with hyperinsulinaemic androgen excess. Scientific Reports, 5(1), 1-12. DOI: 10.1038/srep11496*
Publication	*Samarra, I., Ramos-Molina, B., Queipo-Ortuño, M. I., Tinahones, F. J., Arola, L., Delpino-Rius, A., ... & Canela, N. (2019). Gender-related differences on polyamine metabolome in liquid biopsies by a simple and sensitive two-step liquid-liquid extraction and LC-MS/MS. Biomolecules, 9(12), 779. DOI: 10.3390/biom9120779*

List of up to 5 most relevant previous projects or activities, connected to the subject of this proposal.

Name of Project or Activity	Short description (Max 500 characters)
ALTERNATIVE	*EnvironmentAL Toxicology of chEmical mixtuRes through aN innovATIVE platform based on aged cardiac tissue model – H2020 2021-2024 (www.alternative-project.eu). The project uses a multidisciplinary approach including omics sciences to develop a cardiac tissue model to test cardiotoxicity of environmental exposure to pharmacological and chemical compounds.*
GLOMICAVE	*GLobal OMIC data integration on Animal, Vegetal and Environment sectors – H2020 2020-2024 (www.glomicave.eu). The project aims to combine and analyse different types of omics data to obtain relevant information and discover new links between animal and vegetable genotype and phenotype.*
PREVENTOMICS	*Empowering consumers to PREVENT diet-related diseases through OMICS science – H2020 2018-2021 (www.preventomics.eu). The project opens the door to the personalisation of treatments for the prevention of noncommunicable diseases through nutrition.*
MED4YOUTH	*MEDiterranean enriched diet FOR tackling YOUTH obesity – H2020 2020-2022. The project aims the development of a multicentre clinical study and the application of omics technologies to elucidate the link between the mediterranean diet, the gut microbiota and the beneficial health effects.*
DANTIAN	*Industrial investment and development of bioactive ingredients and new foods for mental health – CIEN 2019-2022. This project, co-funded by the Centro para el Desarrollo Tecnológico e Industrial and FEDER has the objective to meet the demand for alimentary strategies aimed at potential mental well-being and cognitive performance of the consumer, understanding the mechanism of action at the cognitive level and its relationship with the intestinal microbiota.*

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work.

Name of infrastructure of equipment	Short description (Max 300 characters)

COS	*The Centre for Omic Sciences (COS) is part of the integrated Infrastructure for Omic Technologies (IOT) and became part of the Spanish Singular National Scientific and Technological Infrastructures Map (named ICTS).*
LC-QqQ-MS	*Liquid chromatography coupled to triple quadrupole mass spectrometer. Ideal to perform targeted metabolomics that requires high sensibility (i.e., acylcarnitines, tryptophan metabolism).*
LC-QTOF-MS	*Liquid chromatography coupled to quadrupole time-of-flight mass spectrometer. Ideal to perform semi-targeted and untargeted metabolomics (i.e., phenolic compounds, lipidomics).*
1H-NMR 600 MHz	*1H Nuclear magnetic resonance with the possibility to work using CPMG pulse sequences for the measurement of dynamic processes (i.e., lipoproteins)*
Bio-Plex 200	*Equipment that enables the use of multiplexed immunoassay kits to analyse several molecules in a single run (I.e., cytokines, interleukins, growth factors...).*

Gender Equality Plan

Does the organization have a Gender Equality Plan (GEP) covering the elements listed below? (•) Yes ( ) No

Minimum process-related requirements (building blocks) for a GEP

- **Publication:** formal document published on the institution's website and signed by the top management
- **Dedicated resources:** commitment of human resources and gender expertise to implement it.
- **Data collection and monitoring:** sex/gender disaggregated data on personnel (and students for establishments concerned) and annual reporting based on indicators.
- **Training:** Awareness raising/trainings on gender equality and unconscious gender biases for staff and decision-makers.
- **Content-wise, recommended areas** to be **covered** and addressed via concrete measures and targets are:
    - work-life balance and organisational culture;
    - gender balance in leadership and decision-making;
    - gender equality in recruitment and career progression;
    - integration of the gender dimension into research and teaching content;
    - measures against gender-based violence including sexual harassment.

PIC	Legal name
913627869	*PERSEUS BIOMICS*

Short name: PERSEUS BIOMICS

Address

Street	INDUSTRIE PARK 6 BUS 3
Town	TIENEN
Postcode	3300
Country	Belgium
Webpage	www.perseusbiomics.com

Specific Legal Statuses

Legal person	yes
Public body	no
Non-profit	no
International organisation	no
Secondary or Higher education establishment	no
Research organisation	no

SME Data

Based on the below details from the Participant Registry the organisation is an SME (small- and medium-sized enterprise) for the call.

SME self-declared status	31/12/2019	- yes
SME self-assessment	31/12/2019	- yes
SME validation	31/12/2020	- yes

Departments carrying out the proposed work

Department 1

Department name	R&D department	☐ not applicable
	☒ Same as proposing organisation's address	
Street	INDUSTRIE PARK 6 BUS 3	
Town	TIENEN	
Postcode	3300	
Country	Belgium	

Links with other participants

Type of link	Participant

Main contact person

This will be the person the EU services will contact concerning this proposal (e.g. for additional information, invitation to hearings, sending of evaluation results, convocation to start grant preparation). The data in blue is read-only. Details (name, first name and e-mail) of Main Contact persons should be edited in the step "Participants" of the submission wizard.

Title Dr

Gender ◯ Woman ◉ Man ◯ Non Binary

First name* **Volker**

Last name* **Leen**

E-Mail* **volker.leen@perseusbiomics.com**

Position in org. COO

Department R&D department

☐ Same as organisation name

☒ Same as proposing organisation's address

Street INDUSTRIE PARK 6 BUS 3

Town TIENEN

Post code 3300

Country Belgium

Website *Please enter website*

Phone *+xxx xxxxxxxxx*

Phone 2 *+xxx xxxxxxxxx*

Researchers involved in the proposal

Title	First Name	Last Name	Gender	Nationality	E-mail	Career Stage	Role of researcher (in the project)	Reference Identifier	Type of identifier
Prof	Jens	Gundlach	Man	Germany	Jens.gundlach@perseusbiomics.com	Category A Top grade re	Team member		
Dr	Arno	Bouwens	Man	Belgium	Arno.bouwens@perseusbiomics.com	Category C Recognised	Team member		
Dr	Agata	Mlodzinska	Woman	Poland	agata.mlodzinska@perseusbiomics.com	Category C Recognised	Team member		
Dr	Pierre Henri	Ferdinand	Man	France	PierreHenri.Ferdinand@perseusbiomics.com		Team member		
Dr	Volker	Leen	Man	Belgium	Volker.leen@perseusbiomics.com		Team member		

Role of participating organisation in the project

Project management	☐
Communication, dissemination and engagement	☐
Provision of research and technology infrastructure	☒
Co-definition of research and market needs	☒
Civil society representative	☐
Policy maker or regulator, incl. standardisation body	☐
Research performer	☒
Technology developer	☒
Testing/validation of approaches and ideas	☒
Prototyping and demonstration	☒
IPR management incl. technology transfer	☐
Public procurer of results	☐
Private buyer of results	☐
Finance provider (public or private)	☐
Education and training	☐
Contributions from the social sciences or/and the humanities	☐
Other If yes, please specify: (Maximum number of characters allowed: 50)	☐

List of up to 5 publications, widely-used datasets, software, goods, services, or any other achievements relevant to the call content.

Type of achievement	Short description (Max 500 characters)
	N/A

List of up to 5 most relevant previous projects or activities, connected to the subject of this proposal.

Name of Project or Activity	Short description (Max 500 characters)
BeyondSeq	*Genomic Mapping development for human and bacterial genetic analysis*
AdGut	*Genomic Mapping development for Alzheimer biomarker discovery*

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work.

Name of infrastructure of equipment	Short description (Max 300 characters)
High Throughput MAP	*Perseus Biomics High throughput microbiome analysis pipeline*
MAP sample prep	*Perseus Biomics R&D labs for sample handling and DNA extraction for microbiome analysis*

Gender Equality Plan

Does the organization have a Gender Equality Plan (GEP) covering the elements listed below? ○ Yes ◉ No

Minimum process-related requirements (building blocks) for a GEP

- **Publication:** formal document published on the institution's website and signed by the top management
- **Dedicated resources:** commitment of human resources and gender expertise to implement it.
- **Data collection and monitoring:** sex/gender disaggregated data on personnel (and students for establishments concerned) and annual reporting based on indicators.
- **Training:** Awareness raising/trainings on gender equality and unconscious gender biases for staff and decision-makers.
- **Content-wise, recommended areas** to be **covered** and addressed via concrete measures and targets are:
    - work-life balance and organisational culture;
    - gender balance in leadership and decision-making;
    - gender equality in recruitment and career progression;
    - integration of the gender dimension into research and teaching content;
    - measures against gender-based violence including sexual harassment.

PIC	Legal name
905269864	*ARTIFICIAL INTELLIGENCE EXPERT SRL*

Short name: ARTIFICIAL INTELLIGENCE EXPERT SRL

Address

Street	STRADA ALEXANDRU VLAHUTA, BLOC LAMA C, A
Town	CLUJ NAPOCA
Postcode	400310
Country	Romania
Webpage	

Specific Legal Statuses

Legal person	yes
Public body	no
Non-profit	no
International organisation	no
Secondary or Higher education establishment	no
Research organisation	no

SME Data

Based on the below details from the Participant Registry the organisation is an SME (small- and medium-sized enterprise) for the call.

SME self-declared status	21/02/2017	- yes
SME self-assessment	21/02/2017	- yes
SME validation	unknown	

Departments carrying out the proposed work

Department 1

Department name	Research department	☐ not applicable
	☒ Same as proposing organisation's address	
Street	STRADA ALEXANDRU VLAHUTA, BLOC LAMA C, A	
Town	CLUJ NAPOCA	
Postcode	400310	
Country	Romania	

Links with other participants

Type of link	Participant

Main contact person

This will be the person the EU services will contact concerning this proposal (e.g. for additional information, invitation to hearings, sending of evaluation results, convocation to start grant preparation). The data in blue is read-only. Details (name, first name and e-mail) of Main Contact persons should be edited in the step "Participants" of the submission wizard.

Title: Dr

Gender: ○ Woman ◉ Man ○ Non Binary

First name*: **Alexandru**

Last name*: **Floares**

E-Mail*: **alexandru.floares@aie-op.com**

Position in org.: CEO

Department: Research department

☐ Same as organisation name

☒ Same as proposing organisation's address

Street: STRADA ALEXANDRU VLAHUTA, BLOC LAMA C, AP.45

Town: CLUJ NAPOCA

Post code: 400310

Country: Romania

Website: *Please enter website*

Phone: +40729994047

Phone 2: *+xxx xxxxxxxxx*

Other contact persons

First Name	Last Name	E-mail	Phone
Adrian	Zety	adrian.zety@aie-op.com	+xxx xxxxxxxxx

Researchers involved in the proposal

Title	First Name	Last Name	Gender	Nationality	E-mail	Career Stage	Role of researcher (in the project)	Reference Identifier	Type of identifier
Dr	Alexandru	Floares	Man	Romania	alexandru.floares@aie-op.com	Category A Top grade re	Leading	0000-0001-9387-6703	Orcid ID
Dr	Brandusa	Bitel	Woman	Romania	brandusa.bitel@gmail.com	Category B Senior resea	Team member		
Mr	Adrian	Zety	Man	Romania	adrian.zety@aie-op.com	Category D First stage r	Team member		

Role of participating organisation in the project

Project management	☐
Communication, dissemination and engagement	☒
Provision of research and technology infrastructure	☒
Co-definition of research and market needs	☒
Civil society representative	☐
Policy maker or regulator, incl. standardisation body	☒
Research performer	☒
Technology developer	☒
Testing/validation of approaches and ideas	☒
Prototyping and demonstration	☒
IPR management incl. technology transfer	☒
Public procurer of results	☐
Private buyer of results	☐
Finance provider (public or private)	☐
Education and training	☒
Contributions from the social sciences or/and the humanities	☐
Other If yes, please specify: (Maximum number of characters allowed: 50)	☐

List of up to 5 publications, widely-used datasets, software, goods, services, or any other achievements relevant to the call content.

Type of achievement	Short description (Max 500 characters)
Publication	*The Smallest Sample Size for the Desired Diagnosis Accuracy DOI:10.13140/RG.2.2.26920.67842*
Publication	*An Artificial Intelligence Approach to Precision Oncology DOI:10.13140/RG.2.2.29208.39689*
Publication	*Bigger Data Is Better for Molecular Diagnosis Tests Based on Decision Trees DOI:10.1007/978-3-319-40973-3_29*
Publication	*Inferring Transcription Networks from Data DOI: 10.1007/978-3-642-30574-0_20*
Publication	*Using Computational Intelligence to Develop Intelligent Clinical Decision Support Systems DOI: 10.1007/978-3-642-14571-1_20*

List of up to 5 most relevant previous projects or activities, connected to the subject of this proposal.

Name of Project or Activity	Short description (Max 500 characters)
EIT Health Startups Meet Pharma	*We presented aiOMICS, a platform which uses AI to develop the best non- invasive multi-cancer diagnostic and early detection test (99% accuracy for 11 types of cancers) to 5 Big Pharma companies. https://discover.events.com/de/baden-wuerttemberg-region/heidelberg/e/freizeit/demo-day-2019-eit-health-startups-meet-pharma-marsilius-310676872*
EIT Health Digital Sandbox	*We were chosen from around 30 applicants received funding and support that helped us in the development of relevant products and services through the involvement of, and collaboration with biobanks, sample holders and health registers in Europe. https://www.mynewsdesk.com/se/eit-health-scandinavia/news/ten-start-ups-granted-funding-to-leverage-health-data-business-opportunities-384439*
AWS AI Challenge	*We were selected among the most innovative AI companies singled out in the first edition of AWS AI Challenge organized by Vestbee in partnership with Amazon Web Services (AWS). https://www.vestbee.com/blog/articles/aws-ai-challenge-meet-top-innovative-ai-solutions*
IntelMark2.0	*We received funding to develop our platform agnostic molecular diagnostic platform. https://www.agerpres.ro/ots/2020/08/11/demararea-proiectului-intelmark-2-0--641982*
SAIA's projects	*The parent organization of AIE, individual projects can be consulted here http://saia-institute.org/blog/*

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work.

Name of infrastructure of equipment	Short description (Max 300 characters)

AIE's computing structure	*Cluster of 16 servers, with shared files system, storage space of 24 TB, RAM 2 TB, 32 CPU and 6 GPU, with MESOS integration software packages.* *Workstations:* • *Lambda's TensorBook (mobile Deep Learning workstation) i7-9750H Processor, 64 GB RAM, RTX 2080 GPU.*
AIE's computing structure	• *2 Lenovo workstations with 32 core, 128 Gb RAM* • *1 mobile Lenovo workstation with 32 Gb RAM* • *2 HP workstations with 28 Gb RAM* *AI-platform integrating multiple open sources Python and R packages.*
Amazon Cloud Services	*AIE won a 100K EUR grant that can be used for Amazon's Cloud services including Cloud Computing in AWS Activate program.*

Gender Equality Plan

Does the organization have a Gender Equality Plan (GEP) covering the elements listed below? ○ Yes ◉ No

Minimum process-related requirements (building blocks) for a GEP

- **Publication:** formal document published on the institution's website and signed by the top management
- **Dedicated resources:** commitment of human resources and gender expertise to implement it.
- **Data collection and monitoring:** sex/gender disaggregated data on personnel (and students for establishments concerned) and annual reporting based on indicators.
- **Training:** Awareness raising/trainings on gender equality and unconscious gender biases for staff and decision-makers.
- **Content-wise, recommended areas** to be **covered** and addressed via concrete measures and targets are:
    - work-life balance and organisational culture;
    - gender balance in leadership and decision-making;
    - gender equality in recruitment and career progression;
    - integration of the gender dimension into research and teaching content;
    - measures against gender-based violence including sexual harassment.

PIC	Legal name
886506281	*mama health technologies GmbH*

Short name: mama health

Address

Street	Karl-Liebknecht-Str. 34, 10178 Berlin
Town	Berlin
Postcode	10178
Country	Germany
Webpage	mamahealth.io

Specific Legal Statuses

Legal person	yes
Public body	no
Non-profit	no
International organisation	no
Secondary or Higher education establishment	no
Research organisation	no

SME Data

Based on the below details from the Participant Registry the organisation is an SME (small- and medium-sized enterprise) for the call.

SME self-declared status	07/04/2022 - yes
SME self-assessment	unknown
SME validation	unknown

Departments carrying out the proposed work

Department 1

Department name	Research department	☐ not applicable
	☒ Same as proposing organisation's address	
Street	Karl-Liebknecht-Str. 34, 10178 Berlin	
Town	Berlin	
Postcode	10178	
Country	Germany	

Links with other participants

Type of link	Participant

Main contact person

This will be the person the EU services will contact concerning this proposal (e.g. for additional information, invitation to hearings, sending of evaluation results, convocation to start grant preparation). The data in blue is read-only. Details (name, first name and e-mail) of Main Contact persons should be edited in the step "Participants" of the submission wizard.

Title: Mr

Gender: ○ Woman ◉ Man ○ Non Binary

First name*: **Mattia Marco**

Last name*: **Caruson**

E-Mail*: **mattia@mamahealth.io**

Position in org.: CEO

Department: mama health technologies GmbH

☒ Same as organisation name

☒ Same as proposing organisation's address

Street: Karl-Liebknecht-Str. 34, 10178 Berlin

Town: Berlin

Post code: 10178

Country: Germany

Website: *Please enter website*

Phone: +39 3292778072

Phone 2: *+xxx xxxxxxxxx*

Researchers involved in the proposal

Title	First Name	Last Name	Gender	Nationality	E-mail	Career Stage	Role of researcher (in the project)	Reference Identifier	Type of identifier
Dr	Adriatik	Nikaj	Man	Albania	adriatik.nikaj@mamahealth.io	Category C Recognised	Team member		
Mr	Jonas	Witt	Man	Germany	jonas.witt@mamahealth.io		Team member		
Mr	Mattia	Caruson	Man	Italy	mattia@mamahealth.io		Leading		
Ms	Abigail	Sidibe	Woman	United States	abby.sidibe@mamahealth.io		Team member		

Role of participating organisation in the project

Project management	☒
Communication, dissemination and engagement	☐
Provision of research and technology infrastructure	☒
Co-definition of research and market needs	☐
Civil society representative	☐
Policy maker or regulator, incl. standardisation body	☐
Research performer	☒
Technology developer	☒
Testing/validation of approaches and ideas	☐
Prototyping and demonstration	☒
IPR management incl. technology transfer	☐
Public procurer of results	☐
Private buyer of results	☐
Finance provider (public or private)	☐
Education and training	☐
Contributions from the social sciences or/and the humanities	☐
Other If yes, please specify: (Maximum number of characters allowed: 50)	☐

List of up to 5 publications, widely-used datasets, software, goods, services, or any other achievements relevant to the call content.

Type of achievement	Short description (Max 500 characters)
Publication	*- Dorina Bano, Adriatik Nikaj, Mathias Weske: Discovering Business Process Architectures from Event Logs. BPM 2021: 162-177* *This is a very recent paper published that abstracts away from discovering an organisation's concrete processes and focuses on mining the overall process architecture that details the relation between all processes in an enterprise. This is one step closer towards the idea of mining cross-organizational processes.*
Publication	*- Adriatik Nikaj, Mathias Weske, Jan Mendling: Semi-automatic derivation of RESTful choreographies from business process choreographies. Softw. Syst. Model. 18(2): 1195-1208 (2019).* *This paper is not explicitly related to healthcare but it shows the usefulness of process choreographies in general. Process choreographies capture the cross-organizational interactions from a global perspective revealing problems that each organization on its own is not aware of.*

List of up to 5 most relevant previous projects or activities, connected to the subject of this proposal.

Name of Project or Activity	Short description (Max 500 characters)
Long Covid	*Mapping the journey of long covid patients to identify the general needs of the patient population and build research studies that help the development of the understanding of how disease impacts human lives.*

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work.

Name of infrastructure of equipment	Short description (Max 300 characters)
Scalable data-processing architecture	*GDPR-complaint data processing architecture.*
Cloud-based chatbot	*A user-friendly tool that allows users to express their health stories freely and without constraints.*
Process mining algorithm	*Through our process mining technology we are able to process a set of individual journeys in order to cluster users based on the similarity of their journeys and provide them insights generated from the wisdom of the crowd.*

Gender Equality Plan

Does the organization have a Gender Equality Plan (GEP) covering the elements listed below? ○ Yes ◉ No

Minimum process-related requirements (building blocks) for a GEP

- **Publication:** formal document published on the institution's website and signed by the top management
- **Dedicated resources:** commitment of human resources and gender expertise to implement it.
- **Data collection and monitoring:** sex/gender disaggregated data on personnel (and students for establishments concerned) and annual reporting based on indicators.
- **Training:** Awareness raising/trainings on gender equality and unconscious gender biases for staff and decision-makers.
- **Content-wise, recommended areas** to be **covered** and addressed via concrete measures and targets are:
    - work-life balance and organisational culture;
    - gender balance in leadership and decision-making;
    - gender equality in recruitment and career progression;
    - integration of the gender dimension into research and teaching content;
    - measures against gender-based violence including sexual harassment.

PIC	Legal name
991346015	*PROTOBIOS OU*

Short name: PROTOBIOS

Address

Street	MAEALUSE 4
Town	TALLINN
Postcode	12618
Country	Estonia
Webpage	

Specific Legal Statuses

Legal person	yes
Public body	no
Non-profit	no
International organisation	no
Secondary or Higher education establishment	no
Research organisation	no

SME Data

Based on the below details from the Participant Registry the organisation is an SME (small- and medium-sized enterprise) for the call.

SME self-declared status	31/12/2019	- yes
SME self-assessment	31/12/2019	- yes
SME validation	03/11/2003	- yes

Departments carrying out the proposed work

Department 1

Department name	Research department	☐ not applicable
	☒ Same as proposing organisation's address	
Street	MAEALUSE 4	
Town	TALLINN	
Postcode	12618	
Country	Estonia	

Links with other participants

Type of link	Participant

Main contact person

This will be the person the EU services will contact concerning this proposal (e.g. for additional information, invitation to hearings, sending of evaluation results, convocation to start grant preparation). The data in blue is read-only. Details (name, first name and e-mail) of Main Contact persons should be edited in the step "Participants" of the submission wizard.

Title: Dr

Gender: (•) Woman ( ) Man ( ) Non Binary

First name*: **Kaia**

Last name*: **Palm**

E-Mail*: **kaia@protobios.com**

Position in org.: CEO

Department: Research department

☐ Same as organisation name

☒ Same as proposing organisation's address

Street: MAEALUSE 4

Town: TALLINN

Post code: 12618

Country: Estonia

Website: *Please enter website*

Phone: +372 55535773

Phone 2: *+xxx xxxxxxxxx*

Other contact persons

First Name	Last Name	E-mail	Phone
Tonis	Timmusk	tonis@protobios.com	+xxx xxxxxxxxx

Researchers involved in the proposal

Title	First Name	Last Name	Gender	Nationality	E-mail	Career Stage	Role of researcher (in the project)	Reference Identifier	Type of identifier
Dr	Kaia	Palm	Woman	Estonia	kaia@protobios.com	Category A Top grade re	Leading	0000-0001-9981-3180	Orcid ID
Dr	Helle	Sadam	Woman	Estonia	helle@protobios.com	Category A Top grade re	Team member		
Prof	Tonis	Timmusk	Man	Estonia	tonis@protobios.com	Category A Top grade re	Team member	0000-0002-1015-3348	Orcid ID
Dr	Hendrik	Pavel	Man	Estonia	hendrikp@exemplas.com		Team member		

Role of participating organisation in the project

Project management	☐
Communication, dissemination and engagement	☐
Provision of research and technology infrastructure	☒
Co-definition of research and market needs	☐
Civil society representative	☐
Policy maker or regulator, incl. standardisation body	☐
Research performer	☒
Technology developer	☒
Testing/validation of approaches and ideas	☐
Prototyping and demonstration	☐
IPR management incl. technology transfer	☐
Public procurer of results	☐
Private buyer of results	☐
Finance provider (public or private)	☐
Education and training	☐
Contributions from the social sciences or/and the humanities	☐
Other If yes, please specify: (Maximum number of characters allowed: 50)	☐

List of up to 5 publications, widely-used datasets, software, goods, services, or any other achievements relevant to the call content.

Type of achievement	Short description (Max 500 characters)
Publication	*Rähni, A. et al. Melanoma-specific antigen-associated antitumor antibody reactivity as immune-related biomarker for targeted immunotherapies. Communications Medicine accepted (2022).*
Publication	*Jaago, M. et al. Antibody response to oral biofilm is a biomarker for acute coronary syndrome in periodontal disease. Commun Biol 5, 205, doi:10.1038/s42003-022-03122-4 (2022).*
Publication	*Pupina, N. et al. Immune response to a conserved enteroviral epitope of the major capsid VP1 protein is associated with lower risk of cardiovascular disease. EBioMedicine 76, 103835, doi:10.1016/j.ebiom.2022.103835 (2022).*
Publication	*Sadam, H. et al. Identification of two highly antigenic epitope markers predicting multiple sclerosis in optic neuritis patients. EBioMedicine 64, 103211, doi:10.1016/j.ebiom.2021.103211 (2021).*
Publication	*Sadam, H. et al. Prostaglandin D2 Receptor DP1 Antibodies Predict Vaccine-induced and Spontaneous Narcolepsy Type 1: Large-scale Study of Antibody Profiling. EBioMedicine 29, 47-59, doi:10.1016/j.ebiom.2018.01.043 (2018).*

List of up to 5 most relevant previous projects or activities, connected to the subject of this proposal.

Name of Project or Activity	Short description (Max 500 characters)
LONG COVID	*EU101057553): Decision support for prediction and management of Long Covid Syndrome (LCS), HORIZON RIA, HLTH-2021-DISEASE-04-07, 01062022-31052026; a large international consortia that is coordinated by Helsinki University Hospital, Finland, and K.Palm/Protobios leads the WP of translational studies on biomarkers of the Long Covid syndrome*
GDNF UpReg	*(NEURON_NDD-198): Glial Cell Line-Derived Neurotrophic Factor (GDNF) promoting schizophrenia: a promising target for innovative treatment, ERA-NET NEURON Cofund2, 13122021- 30112024; Protobios leads the subproject on auto-immune CSF and serum antibody epitopes in FEP patients receiving novel treatments together with clinicians from Dept. of Psychiatry and Psychotherapy, LMU, Germany*
cGEM	*(EU810645): Center for Genomics, Evolution and Medicine; to advance personalized medicine solutions for disease prevention, diagnostics and treatment, HORIZON RIA, 01092018-31082023; Protobios leads the subproject on non-invasive genetic testing by use of MVA on the Estonian Biobank samples*
SZTEST	*Biomarker development for early diagnosis of mental disease, EU, H2020-MSCA-RISE-2017; 01012017-30062022; an international academy-industry consortia where Protobios is the coordinator and leads the WP on development of blood test for early detection of schizophrenia*
PanBioRA	*(EU760921): Personalized and/or generalized integrated biomaterial risk assessment, H2020-NMBP-2017: 01012017-31122021; a large international academy-industry consortia where Protobios did the MVA protocol development for risk assessment of biomaterials to individuals with chronic conditions*

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work.

Name of infrastructure of equipment	Short description (Max 300 characters)
	PB's analysis laboratory is accredited with ISO 17025, offering a high-quality bioanalytical service for qualitative and quantitative analysis across a variety of matrices. State-of-the-art lab facilities equipped with Robotic Printer Spotter (Arrayit).

	Luminex FlexMap3D clinical diagnostics multiplexed assay high- throughput instrument (Luminex), high- throughput transfection equipment (Lonza Nucleofector), image analysis equipment Ettan DIGE Imager (Ge Healthcare Life Sciences).

Gender Equality Plan

Does the organization have a Gender Equality Plan (GEP) covering the elements listed below? ○ Yes ◉ No

Minimum process-related requirements (building blocks) for a GEP

- **Publication:** formal document published on the institution's website and signed by the top management
- **Dedicated resources:** commitment of human resources and gender expertise to implement it.
- **Data collection and monitoring:** sex/gender disaggregated data on personnel (and students for establishments concerned) and annual reporting based on indicators.
- **Training:** Awareness raising/trainings on gender equality and unconscious gender biases for staff and decision-makers.
- **Content-wise, recommended areas** to be **covered** and addressed via concrete measures and targets are:
    - work-life balance and organisational culture;
    - gender balance in leadership and decision-making;
    - gender equality in recruitment and career progression;
    - integration of the gender dimension into research and teaching content;
    - measures against gender-based violence including sexual harassment.

PIC	Legal name
888675007	*Cephalgo*

Short name: Cephalgo

Address

Street	8 rue des Veaux
Town	Strasbourg
Postcode	67000
Country	France
Webpage	https://cephalgo.com

Specific Legal Statuses

Legal person	yes
Public body	no
Non-profit	no
International organisation	no
Secondary or Higher education establishment	no
Research organisation	no

SME Data

Based on the below details from the Participant Registry the organisation is an SME (small- and medium-sized enterprise) for the call.

SME self-declared status	04/11/2021 - yes
SME self-assessment	unknown
SME validation	unknown

Departments carrying out the proposed work

Department 1

Department name	Research Department	☐ not applicable
	☒ Same as proposing organisation's address	
Street	8 rue des Veaux	
Town	Strasbourg	
Postcode	67000	
Country	France	

Links with other participants

Type of link	Participant

Main contact person

This will be the person the EU services will contact concerning this proposal (e.g. for additional information, invitation to hearings, sending of evaluation results, convocation to start grant preparation). The data in blue is read-only. Details (name, first name and e-mail) of Main Contact persons should be edited in the step "Participants" of the submission wizard.

Title: Dr

Gender: (•) Woman ( ) Man ( ) Non Binary

First name*: **Lisa**

Last name*: **Chiang**

E-Mail*: **lisa.chiang@cephalgo.com**

Position in org.: CEO

Department: Research Department

☐ Same as organisation name

☒ Same as proposing organisation's address

Street: 8 rue des Veaux

Town: Strasbourg

Post code: 67000

Country: France

Website: *Please enter website*

Phone: +33788408506

Phone 2: *+xxx xxxxxxxxx*

Researchers involved in the proposal

Title	First Name	Last Name	Gender	Nationality	E-mail	Career Stage	Role of researcher (in the project)	Reference Identifier	Type of identifier
Dr	Jonathan	Chardin	Man	France	jonathan.chardin@cephalgo.com	Category B Senior resea	Team member		
Dr	Caroline	Correia	Woman	France	caroline.correia@cephalgo.com	Category C Recognised	Team member		
Dr	Lisa Hsin-Yin	Chiang	Woman	Taiwan	lisa.chiang@cephalgo.com	Category B Senior resea	Leading		
Mr	Liang	Chen	Man	Taiwan	liang.chen@cephalgo.com	Category D First stage r	Team member		

Role of participating organisation in the project

Project management	☒
Communication, dissemination and engagement	☒
Provision of research and technology infrastructure	☒
Co-definition of research and market needs	☒
Civil society representative	☐
Policy maker or regulator, incl. standardisation body	☐
Research performer	☒
Technology developer	☒
Testing/validation of approaches and ideas	☒
Prototyping and demonstration	☒
IPR management incl. technology transfer	☐
Public procurer of results	☐
Private buyer of results	☐
Finance provider (public or private)	☐
Education and training	☒
Contributions from the social sciences or/and the humanities	☐
Other If yes, please specify: (Maximum number of characters allowed: 50)	☐

List of up to 5 publications, widely-used datasets, software, goods, services, or any other achievements relevant to the call content.

Type of achievement	Short description (Max 500 characters)
Publication	*Zheng, W. L., & Lu, B. L. (2015). Investigating critical frequency bands and channels for EEG-based emotion recognition with deep neural networks. IEEE Transactions on Autonomous Mental Development, 7(3), 162-175. 10.1109/TAMD.2015.2431497*
Publication	*Wang, X., Sun, X., Gan, D., Soubrier, M., Chiang, H. Y., Yan, L., ... & Lu, X. (2022). Bioadhesive and conductive hydrogel-integrated brain-machine interfaces for conformal and immune-evasive contact with brain tissue. Matter. 10.1016/j.matt.2022.01.012*
Publication	*Newson, J. J., & Thiagarajan, T. C. EEG Frequency Bands in Psychiatric Disorders: A Review of Resting State Studies. Front Hum Neurosci. 2018; 12: 521. Epub 2019/01/29. https://doi.org/10.3389/fnhum. 2018.00521 PMID: 30687041.*
Publication	*Zheng, W. L., & Lu, B. L. (2015). Investigating critical frequency bands and channels for EEG-based emotion recognition with deep neural networks. IEEE Transactions on Autonomous Mental Development, 7(3), 162-175. 10.1109/TAMD.2015.2431497*
Publication	*Koelstra, S., Muhl, C., Soleymani, M., Lee, J. S., Yazdani, A., & Ebrahimi, T. & Patras, I.(2011). Deap: A database for emotion analysis; using physiological signals. IEEE transactions on affective computing, 3(1). 10.1109/T-AFFC.2011.15*

List of up to 5 most relevant previous projects or activities, connected to the subject of this proposal.

Name of Project or Activity	Short description (Max 500 characters)
Hydrogel-based Electrode Innovation	*Together with Technical University of Munich, Cephalgo develops a new type of EEG dry electrode featuring conductive hydrogel, providing steady signal acquisition due to its skin adhesion, hydrophilicity (applicable with extensive sweat), good conductance, and physical robustness (lifetime over 6 months). With such a dry electrode, Cephalgo is able to eliminate motion artefacts during EEG acquisition and enable patient monitoring in every occasion, e.g. at work or during sports.*
Real time Emotion Analysis Using Edge Computation	*Cephalgo works with National Tsing Hua University in developing a hybrid computation system. This edge computing will be implemented on Cephalgo's app for patients so that every patient is able to see a lite emotion result in real time to boost self engagement in emotion labelling. In parallel, Cephalgo's platform for psychiatrists will be powered by hybrid computation with edge computing implemented on local computing units (PC, mobile phone, laptop, etc.).*

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work.

Name of infrastructure of equipment	Short description (Max 300 characters)
	N/A

Gender Equality Plan

Does the organization have a Gender Equality Plan (GEP) covering the elements listed below? ○ Yes ◉ No

Minimum process-related requirements (building blocks) for a GEP

- **Publication:** formal document published on the institution's website and signed by the top management
- **Dedicated resources:** commitment of human resources and gender expertise to implement it.
- **Data collection and monitoring:** sex/gender disaggregated data on personnel (and students for establishments concerned) and annual reporting based on indicators.
- **Training:** Awareness raising/trainings on gender equality and unconscious gender biases for staff and decision-makers.
- **Content-wise, recommended areas** to be **covered** and addressed via concrete measures and targets are:
    - work-life balance and organisational culture;
    - gender balance in leadership and decision-making;
    - gender equality in recruitment and career progression;
    - integration of the gender dimension into research and teaching content;
    - measures against gender-based violence including sexual harassment.

PIC	Legal name
952764653	*BIOKERALTY RESEARCH INSTITUTE AIE*

Short name: BIOKERALTY

Address

Street	ENTIDAD ARCAUTE 005 ARCAUTE
Town	ARCAUTE ALAVA
Postcode	01192
Country	Spain
Webpage	www.biokeralty.com

Specific Legal Statuses

Legal person	yes
Public body	no
Non-profit	yes
International organisation	no
Secondary or Higher education establishment	no
Research organisation	no

SME Data

Based on the below details from the Participant Registry the organisation is not an SME (small- and medium-sized enterprise) for the call.

SME self-declared status	15/05/2018 - no
SME self-assessment	unknown
SME validation	unknown

Departments carrying out the proposed work

No department involved

Department name *Name of the department/institute carrying out the work.*

☒ not applicable

☐ Same as proposing organisation's address

Street *Please enter street name and number.*

Town *Please enter the name of the town.*

Postcode *Area code.*

Country *Please select a country*

Links with other participants

Type of link	Participant

Main contact person

This will be the person the EU services will contact concerning this proposal (e.g. for additional information, invitation to hearings, sending of evaluation results, convocation to start grant preparation). The data in blue is read-only. Details (name, first name and e-mail) of Main Contact persons should be edited in the step "Participants" of the submission wizard.

Title Mr

Gender ◯ Woman ◉ Man ◯ Non Binary

First name* **Angel**

Last name* **Del Pozo**

E-Mail* **angel.delpozo@keralty.com**

Position in org. Deputy Manager of R&D&I Programmes strategy

Department BIOKERALTY RESEARCH INSTITUTE AIE

☒ Same as organisation name

☒ Same as proposing organisation's address

Street ENTIDAD ARCAUTE 005 ARCAUTE

Town ARCAUTE ALAVA

Post code 01192

Country Spain

Website *Please enter website*

Phone *+xxx xxxxxxxxx*

Phone 2 *+xxx xxxxxxxxx*

Other contact persons

First Name	Last Name	E-mail	Phone
Unai	Mancisidor	unai.mancisidor@keralty.com	+xxx xxxxxxxxx

Researchers involved in the proposal

Title	First Name	Last Name	Gender	Nationality	E-mail	Career Stage	Role of researcher (in the project)	Reference Identifier	Type of identifier
Mrs	Oihane	Ibarrola	Woman	Spain	oihane.ibarrola@keralty.com	Category C Recognised	Team member	0000-0002-9089-6925	Orcid ID
Mrs	Catalina	Martínez	Woman	Spain	catalina.martinez@keralty.com	Category D First stage r	Leading	0000-0002-8473-4065	Orcid ID
Mr	Angel	Del Pozo	Man	Spain	angel.delpozo@keralty.com	Category B Senior resea	Team member	0000-0002-2211-9200	Orcid ID

Role of participating organisation in the project

Project management	☐
Communication, dissemination and engagement	☒
Provision of research and technology infrastructure	☐
Co-definition of research and market needs	☐
Civil society representative	☐
Policy maker or regulator, incl. standardisation body	☐
Research performer	☒
Technology developer	☐
Testing/validation of approaches and ideas	☐
Prototyping and demonstration	☐
IPR management incl. technology transfer	☐
Public procurer of results	☐
Private buyer of results	☐
Finance provider (public or private)	☐
Education and training	☒
Contributions from the social sciences or/and the humanities	☐
Other If yes, please specify: (Maximum number of characters allowed: 50)	☐

List of up to 5 publications, widely-used datasets, software, goods, services, or any other achievements relevant to the call content.

Type of achievement	Short description (Max 500 characters)
Publication	*Gainza, E., Villullas, S., Ibarrola, O., Gainza, G., Herrán, E., Aguirre, J.J., Del Pozo, A., Pedraz, J.L., Esquisabel, A., Moreno, M., Pastor, M., Viñas, M., Vinuesa, T., Bachiller, D. Tittle: Tobramycin-loaded nanostructured lipid carriers (NLC (P201431894). Priority Country: Spain Date: 19/12/2014 Other countries: Europe, Brasil, Colombia, EEUU.*
Publication	*Gainza, E., Del Pozo, A., Gainza, G., Ibarrola, O., Villullas, S., Fernández, R., Bachiller, D., Pedraz, J.L., Esquisabel, A., Pastor, M., Fuste, E., Sans, E. and Gil, I. Tittle: Polymyxin-loaded nanostructured lipid carriers (13382268) Priority country: España Date: 04/07/2013 Other countries: Europe (Spain, Italy, France, Germany, UK) and EEUU.*
Publication	*Vairo C, Basas J, Pastor M, Palau M, Gomis X, Almirante B, Gainza E, Hernandez RM, Igartua M, Gavaldà J, Gainza G. In vitro and in vivo antimicrobial activity of sodium colistimethate and amikacin-loaded nanostructured lipid carriers (NLC). Nanomedicine. 2020 Oct;29:102259. doi: 10.1016/j.nano.2020.102259. Epub 2020 Jul 1. PMID: 32619707.*
Publication	*Chato-Astrain J, Chato-Astrain I, Sánchez-Porras D, García-García ÓD, Bermejo-Casares F, Vairo C, Villar-Vidal M, Gainza G, Villullas S, Oruezabal RI, Ponce-Polo Á, Garzón I, Carriel V, Campos F, Alaminos M. Generation of a novel human dermal substitute functionalized with antibiotic-loaded nanostructured lipid carriers (NLCs) with antimicrobial properties for tissue engineering. J Nanobiotechnology. 2020 Nov 23;18(1):174. doi: 10.1186/s12951-020-00732-0. PMID: 33228673; PMCID: PMC7686763.*
Publication	*Carreira-Barral I , Rumbo C , Mielczarek M , Alonso-Carrillo D , Herran E , Pastor M , Del Pozo A , García-Valverde M , Quesada R . Small molecule anion transporters display in vitro antimicrobial activity against clinically relevant bacterial strains. Chem Commun (Camb). 2019 Aug 20;55(68):10080-10083. doi: 10.1039/c9cc04304g. PMID: 31380526.*

List of up to 5 most relevant previous projects or activities, connected to the subject of this proposal.

Name of Project or Activity	Short description (Max 500 characters)
SAFE-N-MEDTECH (2019-2023) H2020	*Safety testing in the life cycle of nanotechnology-enabled medical technologies for health*
NOCANTHER (2016-2021) H2020	*Nanomedicine upscaling for early clinical phases of multimodal cancer therapy*
SMART-4-FABRY (2017-2020) H2020	*Smart multifunctional GLA-nanoformulation for Fabry disease*
TAT-CF (2016-2018) H2020	*Novel therapeutic approaches for the treatment of cystic fibrosis based on small molecule transmembrane anion transporters*
REFINE (2017-2022) H2020	*Regulatory Science Framework for Nano(bio)material-based Medical Products and Devices*

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work.

Name of infrastructure of equipment	Short description (Max 300 characters)

	Pilot plant for the production of magnetic nanoparticles (2L reactor)
	Solid Lipid Nanoparticles production (using ultrasounds)
	Z sizer, nano characterization equipments
	Cell culture equipment (incubator, ultra-freezer, laminar flow hood…)

Gender Equality Plan

Does the organization have a Gender Equality Plan (GEP) covering the elements listed below? (•) Yes ( ) No

Minimum process-related requirements (building blocks) for a GEP

- **Publication:** formal document published on the institution's website and signed by the top management
- **Dedicated resources:** commitment of human resources and gender expertise to implement it.
- **Data collection and monitoring:** sex/gender disaggregated data on personnel (and students for establishments concerned) and annual reporting based on indicators.
- **Training:** Awareness raising/trainings on gender equality and unconscious gender biases for staff and decision-makers.
- **Content-wise, recommended areas** to be **covered** and addressed via concrete measures and targets are:
    - work-life balance and organisational culture;
    - gender balance in leadership and decision-making;
    - gender equality in recruitment and career progression;
    - integration of the gender dimension into research and teaching content;
    - measures against gender-based violence including sexual harassment.

PIC	Legal name
915801736	*Fundación Universitaria Sanitas*

Short name: Fundación Universitaria Sanitas

Address

Street	Calle 100 #11B-67
Town	Bogotá
Postcode	
Country	Colombia
Webpage	www.unisanitas.edu.co

Specific Legal Statuses

Legal person	yes
Public body	no
Non-profit	yes
International organisation	yes
Secondary or Higher education establishment	yes
Research organisation	yes

SME Data

Based on the below details from the Participant Registry the organisation is no (small- and medium-sized enterprise) for the call.

SME self-declared status	unknown
SME self-assessment	unknown
SME validation	unknown

Departments carrying out the proposed work

Department 1

Department name	Clinical Research Department	☐ not applicable
	☐ Same as proposing organisation's address	
Street	Carrera 7 no 173-64	
Town	Bogota	
Postcode	110141	
Country	Colombia	

Links with other participants

Type of link	Participant

Main contact person

This will be the person the EU services will contact concerning this proposal (e.g. for additional information, invitation to hearings, sending of evaluation results, convocation to start grant preparation). The data in blue is read-only. Details (name, first name and e-mail) of Main Contact persons should be edited in the step "Participants" of the submission wizard.

Title Dr

Gender ◯ Woman ◉ Man ◯ Non Binary

First name* **Mario Arturo**

Last name* **Isaza Ruget**

E-Mail* **misaza@keralty.com**

Position in org. Rector

Department Fundación Universitaria Sanitas

☒ Same as organisation name

☒ Same as proposing organisation's address

Street Calle 100 #11B-67

Town Bogotá

Post code

Country Colombia

Website *Please enter website*

Phone *+xxx xxxxxxxxx*

Phone 2 *+xxx xxxxxxxxx*

Other contact persons

First Name	Last Name	E-mail	Phone
Claudia	Aristizabal	claristizabal@unisanitas.edu.co	+xxx xxxxxxxxx

Researchers involved in the proposal

Title	First Name	Last Name	Gender	Nationality	E-mail	Career Stage	Role of researcher (in the project)	Reference Identifier	Type of identifier
Dr	Carlos Arturo	Alvarez Moreno	Man	Colombia	calvarez@colsanitas.com	Category A Top grade re	Leading	0000-0001-5419-4494	Orcid ID
Dr	Juan Javier	López Rivera	Man	Colombia	jjlopez@colsanitas.com	Category D First stage r	Team member		
Dr	Mario Arturo	Isaza Ruget	Man	Colombia	misaza@keralty.com	Category C Recognised	Team member		
Dr	Johana	Vargas	Woman	Colombia	jvargas@colsanitas.com	Category D First stage r	Team member		
Mrs	Claudia	Aristizabal	Woman	Colombia	claristizabal@unisanitas.edu.co		Team member		

Role of participating organisation in the project

Project management	☒
Communication, dissemination and engagement	☒
Provision of research and technology infrastructure	☒
Co-definition of research and market needs	☒
Civil society representative	☐
Policy maker or regulator, incl. standardisation body	☐
Research performer	☐
Technology developer	☐
Testing/validation of approaches and ideas	☐
Prototyping and demonstration	☐
IPR management incl. technology transfer	☐
Public procurer of results	☐
Private buyer of results	☐
Finance provider (public or private)	☐
Education and training	☒
Contributions from the social sciences or/and the humanities	☐
Other If yes, please specify: (Maximum number of characters allowed: 50)	☒

patient search and recruitment, trials conducting

List of up to 5 publications, widely-used datasets, software, goods, services, or any other achievements relevant to the call content.

Type of achievement	Short description (Max 500 characters)
Publication	*Repurposed antiviral drugs for COVID-19 – Interim WHO Solidarity Trial Results. N Engl J Med 2021; 384:497-511. DOI: 10.1056/NEJMoa2023184*
Publication	*Cifuentes MP, Rodriguez-Villamizar LA, Rojas-Botero ML, et al Socioeconomic inequalities associated with mortality for COVID-19 in Colombia: a cohort nationwide study J Epidemiol Community Health Published Online First: 04 March 2021. doi: 10.1136/ jech-2020-216275*
Publication	*Clinical course, biomarkers, management and outcomes of patients hospitalised due to covid-19 in colombia Infectio 25, 4: 04 2021. doi: 10.22354/in.v25i4.958*
Publication	*Ambulatory care sensitive conditions hospitalization for emergencies rates in Colombia González-Vélez AE, Mejía CCC, Padilla EL, Marín SYM, Bobadilla PAR, Sánchez JPR, et al. Ambulatory care sensitive conditions hospitalization for emergencies rates in Colombia. Rev Saude Publica. 2019; 53:36. DOI: 10.11606/S1518-8787.2019053000563*

List of up to 5 most relevant previous projects or activities, connected to the subject of this proposal.

Name of Project or Activity	Short description (Max 500 characters)
	Effectiveness and safety of medical treatment for SARS by COVID-19, Colombia. Pragmatic randomized controlled study. Clinical trial whose main objective is to evaluate effectiveness and safety of different medical treatments used in clinical practice for the management of hospitalized patients with SARS-Cov-2
INNO4COV-19	*INNO4COV-19 Project aims to support the full development to market uptake of technologies at TRL6 or higher. To achieve this, the project provides funding to third parties.INNO4COV-19 Project addresses the need for diagnosis prognosis and monitoring systems targeting COVID-19, with increased efficacy, efficiency and at a lower cost. https://cordis.europa.eu/project/id/101016203/es*
SAFE-N-MEDTECH	*We are building an innovative open access platform to offer companies and reference laboratories, the capabilities, knowhow, networks and services required for the development, testing, assessment, upscaling and market exploitation of nanotechnology-based Medical and Diagnosis Devices. https://cordis.europa.eu/project/id/814607/es*

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work.

Name of infrastructure of equipment	Short description (Max 300 characters)
Laboratories	*Laboratories of Biochemistry, Histology, Physiology, Anatomy and Pathology. Molecular biology*
Clinical Trials Unit	*i) two consulting rooms; (ii) two offices for the clinical study coordinators and a meeting room for monitoring activities;*

Clinical Trials Unit	*(iii) an exclusive area for storage of the research product at controlled room temperature and in cold chain from 2°C to 8°C, with continuous monitoring system of room temperature, refrigeration temperature and relative humidity;*
Clinical Trials Unit	*(iv) Drug preparation center (outsourced with a center certified in Good Manufactured Practice); (v) laboratory sampling area;*
Clinical Trials Unit	*(vi) an exclusive area for laboratory with kits storage at controlled room temperature, sample storage at -20°C or -70°C (as required), sample packing and shipping area, and shipping area, and continuous monitoring system of room temperature, refrigeration temperature and relative humidity;*
Clinical Trials Unit	*(vii) Local processing of samples (Hematology, blood chemistry, hormones, immunology, microscopy, microbiology, molecular biology, pathology)*

Gender Equality Plan

Does the organization have a Gender Equality Plan (GEP) covering the elements listed below? ○ Yes ◉ No

Minimum process-related requirements (building blocks) for a GEP

- **Publication:** formal document published on the institution's website and signed by the top management
- **Dedicated resources:** commitment of human resources and gender expertise to implement it.
- **Data collection and monitoring:** sex/gender disaggregated data on personnel (and students for establishments concerned) and annual reporting based on indicators.
- **Training:** Awareness raising/trainings on gender equality and unconscious gender biases for staff and decision-makers.
- **Content-wise, recommended areas** to be **covered** and addressed via concrete measures and targets are:
    - work-life balance and organisational culture;
    - gender balance in leadership and decision-making;
    - gender equality in recruitment and career progression;
    - integration of the gender dimension into research and teaching content;
    - measures against gender-based violence including sexual harassment.

PIC	Legal name
999898020	*UNIVERSITA DEGLI STUDI DI SIENA*

Short name: UNISI

Address

Street	VIA BANCHI DI SOTTO 55
Town	SIENA
Postcode	53100
Country	Italy
Webpage	www.unisi.it

Specific Legal Statuses

Legal person	yes
Public body	yes
Non-profit	yes
International organisation	no
Secondary or Higher education establishment	yes
Research organisation	yes

SME Data

Based on the below details from the Participant Registry the organisation is not an SME (small- and medium-sized enterprise) for the call.

SME self-declared status	11/11/2008	- no
SME self-assessment	11/11/2008	- no
SME validation	11/11/2008	- no

Departments carrying out the proposed work

Department 1

Department name	DEPARTMENT OF MOLECULAR AND DEVELOPMENTAL MEDICINE	☐ not applicable
	☐ Same as proposing organisation's address	
Street	Via A. MoroPoliclinico Le Scotte,	
Town	Sienna	
Postcode	53100	
Country	Italy	

Links with other participants

Type of link	Participant

Main contact person

This will be the person the EU services will contact concerning this proposal (e.g. for additional information, invitation to hearings, sending of evaluation results, convocation to start grant preparation). The data in blue is read-only. Details (name, first name and e-mail) of Main Contact persons should be edited in the step "Participants" of the submission wizard.

Title Prof.

Gender ○ Woman ◉ Man ○ Non Binary

First name* **Andrea**

Last name* **Fagiolini**

E-Mail* **andrea.fagiolini@unisi.it**

Position in org. Full Professor

Department DEPARTMENT OF MOLECULAR AND DEVELOPMENTAL MEDICINE

☐ Same as organisation name

☐ Same as proposing organisation's address

Street Via A. MoroPoliclinico Le Scotte,

Town Sienna

Post code 53100

Country Italy

Website *Please enter website*

Phone *+xxx xxxxxxxxx*

Phone 2 *+xxx xxxxxxxxx*

Other contact persons

First Name	Last Name	E-mail	Phone
Donata	Franzi	research.eu@unisi.it	+xxx xxxxxxxxx

Researchers involved in the proposal

Title	First Name	Last Name	Gender	Nationality	E-mail	Career Stage	Role of researcher (in the project)	Reference Identifier	Type of identifier
Prof	Andrea	Fagiolini	Man	Italy	andrea.fagiolini@unisi.it		Leading	0000-0001-5827-0853	Orcid ID
Prof	Arianna	Goracci	Woman	Italy	a.goracci@gmail.com		Team member		
Mr	Sabina	Parente	Woman	Italy	sabina.parente@unisi.it		Team member		

Role of participating organisation in the project

Project management	☒
Communication, dissemination and engagement	☒
Provision of research and technology infrastructure	☒
Co-definition of research and market needs	☒
Civil society representative	☐
Policy maker or regulator, incl. standardisation body	☐
Research performer	☒
Technology developer	☐
Testing/validation of approaches and ideas	☒
Prototyping and demonstration	☐
IPR management incl. technology transfer	☐
Public procurer of results	☐
Private buyer of results	☐
Finance provider (public or private)	☐
Education and training	☒
Contributions from the social sciences or/and the humanities	☐
Other If yes, please specify: (Maximum number of characters allowed: 50)	☐

List of up to 5 publications, widely-used datasets, software, goods, services, or any other achievements relevant to the call content.

Type of achievement	Short description (Max 500 characters)
Publication	*A Delphi-method-based consensus guideline for definition of treatment-resistant depression for clinical trials. Mol Psychiatry. 2021 Dec 15. doi: 10.1038/s41380-021-01381-x. Epub ahead of print. PMID: 34907394.*
Publication	*Fagiolini A, Albert U, Ferrando L, Herman E, Muntean C, Pálová E, Cattaneo A, Comandini A, Di Dato G, Di Loreto G, Olivieri L, Salvatori E, Tongiani S, Kasper S. A randomized, double-blind study comparing the efficacy and safety of trazodone once-a-day and venlafaxine extended-release for the treatment of patients with major depressive disorder. Int Clin Psychopharmacol. 2020 May;35(3):137-146. doi: 10.1097/YIC.0000000000000304. PMID: 31972628; PMCID: PMC7099841.*
Publication	*Fagiolini A, Florea I, Loft H, Christensen MC. Effectiveness of Vortioxetine on Emotional Blunting in Patients with Major Depressive Disorder with inadequate response to SSRI/SNRI treatment. J Affect Disord. 2021 Mar 15;283:472-479. doi: 10.1016/j.jad.2020.11.106. Epub 2020 Nov 19. PMID: 33516560.*
Publication	*Daly EJ, Trivedi MH, Janik A, Li H, Zhang Y, Li X, Lane R, Lim P, Duca AR, Hough D, Thase ME, Zajecka J, Winokur A, Divacka I, Fagiolini A, Cubala WJ, Bitter I, Blier P, Shelton RC, Molero P... Efficacy of Esketamine Nasal Spray Plus Oral Antidepressant Treatment for Relapse Prevention in Patients With Treatment-Resistant Depression: A Randomized Clinical Trial. JAMA Psychiatry. 2019 Sep 1;76(9):893-903. doi: 10.1001/jamapsychiatry.2019.1189. PMID: 31166571; PMCID: PMC6551577.*
Publication	*Catena-Dell'Osso M, Rotella F, Dell'Osso A, Fagiolini A, Marazziti D. Inflammation, serotonin and major depression. Curr Drug Targets. 2013 May 1;14(5):571-7. doi: 10.2174/1389450113149990154. PMID: 23531160.*

List of up to 5 most relevant previous projects or activities, connected to the subject of this proposal.

Name of Project or Activity	Short description (Max 500 characters)
	N/A

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work.

Name of infrastructure of equipment	Short description (Max 300 characters)
	N/A

Gender Equality Plan

Does the organization have a Gender Equality Plan (GEP) covering the elements listed below? (•) Yes ( ) No

Minimum process-related requirements (building blocks) for a GEP

- **Publication:** formal document published on the institution's website and signed by the top management
- **Dedicated resources:** commitment of human resources and gender expertise to implement it.
- **Data collection and monitoring:** sex/gender disaggregated data on personnel (and students for establishments concerned) and annual reporting based on indicators.
- **Training:** Awareness raising/trainings on gender equality and unconscious gender biases for staff and decision-makers.
- **Content-wise, recommended areas** to be **covered** and addressed via concrete measures and targets are:
    - work-life balance and organisational culture;
    - gender balance in leadership and decision-making;
    - gender equality in recruitment and career progression;
    - integration of the gender dimension into research and teaching content;
    - measures against gender-based violence including sexual harassment.

PIC	Legal name
915115946	*STICHTING UNIVERSITAIRE EN ALGEMENE KINDER - EN JEUGDPSYCHIATRIE NOORD-NEDERLAND*

Short name: STICHTING UNIVERSITAIRE EN ALGEMENE KINDER - EN JEUGDPSYCHIATRIE NOORD-NEDERLAND

Address

Street	BEILERSTRAAT 173
Town	ASSEN
Postcode	9401 PJ
Country	Netherlands
Webpage	www.accare.nl

Specific Legal Statuses

Legal person	yes
Public body	no
Non-profit	yes
International organisation	no
Secondary or Higher education establishment	no
Research organisation	no

SME Data

Based on the below details from the Participant Registry the organisation is no (small- and medium-sized enterprise) for the call.

SME self-declared status	unknown
SME self-assessment	unknown
SME validation	unknown

Departments carrying out the proposed work

Department 1

Department name	Accare Child Study Center	☐ not applicable
	☐ Same as proposing organisation's address	
Street	Lübeckweg 2	
Town	Groningen	
Postcode	9723 HE	
Country	Netherlands	

Links with other participants

Type of link	Participant

Main contact person

This will be the person the EU services will contact concerning this proposal (e.g. for additional information, invitation to hearings, sending of evaluation results, convocation to start grant preparation). The data in blue is read-only. Details (name, first name and e-mail) of Main Contact persons should be edited in the step "Participants" of the submission wizard.

Title: Prof.

Gender: ○ Woman ◉ Man ○ Non Binary

First name*: **Pieter**

Last name*: **Hoekstra**

E-Mail*: **p.hoekstra@accare.nl**

Position in org.: Full professor and director of research

Department: Accare Child Study Center

☐ Same as organisation name

☐ Same as proposing organisation's address

Street: Lübeckweg 2

Town: Groningen

Post code: 9723 HE

Country: Netherlands

Website: *Please enter website*

Phone: +31612243857

Phone 2: *+xxx xxxxxxxxx*

Researchers involved in the proposal

Title	First Name	Last Name	Gender	Nationality	E-mail	Career Stage	Role of researcher (in the project)	Reference Identifier	Type of identifier
Prof	Pieter	Hoekstra	Man	Netherlands	p.hoekstra@accare.nl	Category A Top grade re	Leading	0000-0003-1018-9954	Orcid ID
Dr	Andrea	Dietrich	Woman	Germany	a.dietrich@accare.nl	Category B Senior resea	Team member	0000-0002-2538-6136	Orcid ID
Prof	Barbara	Van den Hoofdakker	Woman	Netherlands	b.van.den.hoofdakker@accare.nl	Category B Senior resea	Team member	0000-0001-9570-9976	Orcid ID
Dr	Marco	Bottelier	Man	Netherlands	m.bottelier@accare.nl		Team member		

Role of participating organisation in the project

Project management	☐
Communication, dissemination and engagement	☐
Provision of research and technology infrastructure	☐
Co-definition of research and market needs	☐
Civil society representative	☐
Policy maker or regulator, incl. standardisation body	☐
Research performer	☒
Technology developer	☐
Testing/validation of approaches and ideas	☐
Prototyping and demonstration	☐
IPR management incl. technology transfer	☐
Public procurer of results	☐
Private buyer of results	☐
Finance provider (public or private)	☐
Education and training	☒
Contributions from the social sciences or/and the humanities	☐
Other If yes, please specify: (Maximum number of characters allowed: 50)	☐

List of up to 5 publications, widely-used datasets, software, goods, services, or any other achievements relevant to the call content.

Type of achievement	Short description (Max 500 characters)
Publication	*Rosenau PT, Openneer TJC, Matthijssen AM, van de Loo-Neus GHH, Buitelaar JK, van den Hoofdakker BJ, Hoekstra PJ, Dietrich A. Effects of methylphenidate on executive functioning in children and adolescents with ADHD after long-term use: a randomized, placebo-controlled discontinuation study. J Child Psychol Psychiatry. 2021 Dec;62(12):1444-1452. doi: 10.1111/jcpp.13419.*
Publication	*Matthijssen AM, Dietrich A, Bierens M, Kleine Deters R, van de Loo-Neus GHH, van den Hoofdakker BJ, Buitelaar JK, Hoekstra PJ. Effects of Discontinuing Methylphenidate on Strengths and Difficulties, Quality of Life and Parenting Stress. J Child Adolesc Psychopharmacol. 2020 Apr;30(3):159-165. doi: 10.1089/cap.2019.0147.*
Publication	*Matthijssen AM, Dietrich A, Bierens M, Kleine Deters R, van de Loo-Neus GHH, van den Hoofdakker BJ, Buitelaar JK, Hoekstra PJ. Continued Benefits of Methylphenidate in ADHD After 2 Years in Clinical Practice: A Randomized Placebo-Controlled Discontinuation Study. Am J Psychiatry. 2019 Sep 1;176(9):754-762. doi: 10.1176/appi.ajp.2019.18111296.*
Publication	*Ramerman L, de Kuijper G, Scheers T, Vink M, Vrijmoeth P, Hoekstra PJ. Is risperidone effective in reducing challenging behaviours in individuals with intellectual disabilities after 1 year or longer use? A placebo-controlled, randomised, double-blind discontinuation study. J Intellect Disabil Res. 2019 May;63(5):418-428. doi: 10.1111/jir.12584*
Publication	*Schweren L, Hoekstra P, van Lieshout M, Oosterlaan J, Lambregts-Rommelse N, Buitelaar J, Franke B, Hartman C. Long-term effects of stimulant treatment on ADHD symptoms, social-emotional functioning, and cognition. Psychol Med. 2019 Jan;49(2):217-223. doi: 10.1017/S0033291718000545.*

List of up to 5 most relevant previous projects or activities, connected to the subject of this proposal.

Name of Project or Activity	Short description (Max 500 characters)
TIC Genetics	*The Tourette International Collaborative Genetics (TIC Genetics) Study includes scientists and clinicians specialized in Tourette Syndrome (TS) from more than 20 sites across the United States, Europe, and South Korea. The goal of this international study is to identify genetic (inherited) factors that play a role in causing TS and comorbid disorders such as Obsessive-Compulsive Disorder (OCD) and Attention-Deficit/Hyperactivity Disorder (ADHD).*
Eat2BeNice	*This is an EU (Horizon2020)-funded medical consortium that studies the connections between gut microbiota, diet, and exercise to formulate nutrition and lifestyle recommendations for brain health.*
Matrics	*An EU FP7 funded project into paediatric conduct disorders characterised by aggressive traits and/or social impairment: from preclinical research to treatment. Aggression is a basic physiological trait, which can lead to maladjustment, social impairment and crime when expressed in the wrong context. As knowledge about aggression aetiology is limited and current treatment strategies are insufficient, the Aggressotype project is working on closing this gap.*
EMTICS	*The EU FP7 MATRICS consortium examines the influences of early life events / stress on the neurobiological substrates underlying aggression and CU traits. Antisocial behavior has a huge consequence on society resulting in physical, emotional and financial damage. Understanding psychopathy is core to this. The project highlights new ways to approach aggressive, antisocial and psychopathic traits.*

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work.

Name of infrastructure of equipment	Short description (Max 300 characters)

Clinical service	*The Accare Child and Adolescent Psychiatry clinical service has access to over 2000 new child and adolescent patients per year and has a dedicated mood disorder specialty clinic. All facilities are in place to collect biospecimens from children.*

Gender Equality Plan

Does the organization have a Gender Equality Plan (GEP) covering the elements listed below? (•) Yes ( ) No

Minimum process-related requirements (building blocks) for a GEP

- **Publication:** formal document published on the institution's website and signed by the top management
- **Dedicated resources:** commitment of human resources and gender expertise to implement it.
- **Data collection and monitoring:** sex/gender disaggregated data on personnel (and students for establishments concerned) and annual reporting based on indicators.
- **Training:** Awareness raising/trainings on gender equality and unconscious gender biases for staff and decision-makers.
- **Content-wise, recommended areas** to be **covered** and addressed via concrete measures and targets are:
    - work-life balance and organisational culture;
    - gender balance in leadership and decision-making;
    - gender equality in recruitment and career progression;
    - integration of the gender dimension into research and teaching content;
    - measures against gender-based violence including sexual harassment.

PIC	Legal name
997946477	*FUNDACIO INSTITUT D'INVESTIGACIO BIOMEDICA DE GIRONA DOCTOR JOSEP TRUETA*

Short name: IDIBGI-CERCA

Address

Street	CALLE DR. CASTANY SN EDIFICIO DE LA MANCO
Town	GIRONA
Postcode	17190
Country	Spain
Webpage	www.idibgi.org

Specific Legal Statuses

Legal person	yes
Public body	no
Non-profit	yes
International organisation	no
Secondary or Higher education establishment	no
Research organisation	yes

SME Data

Based on the below details from the Participant Registry the organisation is not an SME (small- and medium-sized enterprise) for the call.

SME self-declared status	13/10/1995 - no
SME self-assessment	unknown
SME validation	unknown

Departments carrying out the proposed work

Department 1

Department name	Institut Assistència Sanitària	☐ not applicable
	☒ Same as proposing organisation's address	
Street	CALLE DR. CASTANY SN EDIFICIO DE LA MANC	
Town	GIRONA	
Postcode	17190	
Country	Spain	

Links with other participants

Type of link	Participant

Main contact person

This will be the person the EU services will contact concerning this proposal (e.g. for additional information, invitation to hearings, sending of evaluation results, convocation to start grant preparation). The data in blue is read-only. Details (name, first name and e-mail) of Main Contact persons should be edited in the step "Participants" of the submission wizard.

Title Dr

Gender ◉ Woman ○ Man ○ Non Binary

First name* **Eva**

Last name* **Frigola**

E-Mail* **eva.frigola@ias.cat**

Position in org. Clinical psychologist

Department Institut d'Assistència Sanitària

☐ Same as organisation name

☒ Same as proposing organisation's address

Street CALLE DR. CASTANY SN EDIFICIO DE LA MANCOMUNIDAD 2 PARQUE HOSPITA

Town GIRONA

Post code 17190

Country Spain

Website *Please enter website*

Phone *+xxx xxxxxxxxx*

Phone 2 *+xxx xxxxxxxxx*

Researchers involved in the proposal

Title	First Name	Last Name	Gender	Nationality	E-mail	Career Stage	Role of researcher (in the project)	Reference Identifier	Type of identifier
Dr	Eva	Frigola Capell	Woman	Spain	eva.frigola@ias.cat	Category B Senior resea	Leading	0000-0003-4758-0316	Orcid ID
Dr	Jordi	Cid	Man	Spain	jordi.cid@ias.cat	Category A Top grade re	Team member	0000-0002-6406-0585	Orcid ID
Dr	Jordi	Font	Man	Spain	jordi.font@ias.cat	Category C Recognised	Team member	0000-0002-5400-5873	Orcid ID
Prof	Ramon	Brugada	Man	Spain	rbrugada@idibgi.org	Category A Top grade re	Team member	0000-0001-6607-3032	Orcid ID
Dr	Carles	Ferrer	Man	Spain	cferrer@gencardio.com	Category B Senior resea	Team member		
Dr	Mónica	Coll	Woman	Spain	mcoll@gencardio.com	Category B Senior resea	Team member	0000-0003-1214-803X	Orcid ID
Dr	Bernat	Del Olmo	Man	Spain	bdelolmo@gencardio.com	Category B Senior resea	Team member	0000-0002-7109-7626	Orcid ID
Ms	Alexandra	Perez	Woman	Spain	aperez@idibgi.org	Category D First stage r	Team member	0000-0001-5344-6573	Orcid ID
Mr	René Ricardo	Morgan-Ferrando	Man	Spain	rene.morgan@ias.cat		Team member	0000-0002-5400-5873	Orcid ID
Ms	Sacramento	Mayoral	Woman	Spain	sacramento.mayoral@ias.cat		Team member		
Ms	Montse	Sitjas	Woman	Spain	montse.sitjas@ias.cat		Team member	0000-0001-6393-794X	Orcid ID
Ms	Pilar	González	Woman	Spain	mariap.gonzalez@ias.cat		Team member		
Ms	Pilar	Ramiro	Woman	Spain	pilar.ramiro@ias.cat		Team member		
Ms	Lourdes	Marquez	Woman	Spain	lourdes.marquez@ias.cat		Team member		
Ms	Patricia	Revilla	Woman	Spain	patricia.revilla@ias.cat		Team member		
Ms	Margarita	De Castro - Palomino	Woman	Spain	margarita.decastro@ias.cat		Team member		

Role of participating organisation in the project

Project management	☒
Communication, dissemination and engagement	☒
Provision of research and technology infrastructure	☒
Co-definition of research and market needs	☐
Civil society representative	☐
Policy maker or regulator, incl. standardisation body	☐
Research performer	☒
Technology developer	☐
Testing/validation of approaches and ideas	☒
Prototyping and demonstration	☐
IPR management incl. technology transfer	☐
Public procurer of results	☐
Private buyer of results	☐
Finance provider (public or private)	☐
Education and training	☐
Contributions from the social sciences or/and the humanities	☒
Other If yes, please specify: (Maximum number of characters allowed: 50)	☐

List of up to 5 publications, widely-used datasets, software, goods, services, or any other achievements relevant to the call content.

Type of achievement	Short description (Max 500 characters)
Publication	*Berta Moreno-Küstner,Julia Fábrega-Ruz,Juan Luis Gonzalez-Caballero,Sara Reyes-Martin,Susana Ochoa,Cristina Romero-Lopez-Alberca,Jordi Cid,Regina Vila-Badia,Eva Frigola-Capell,Luis Salvador-Carulla. Patient-reported impact of symptoms in schizophrenia scale (PRISS): Development and validation. Acta Psychiatrica Scandinavicaournal (early view): 2022*
Publication	*Sastre-Buades A, Ochoa S, Lorente-Rovira E, Barajas A, Grasa E, López-Carrilero R, Luengo A, Ruiz-Delgado I, Cid J, González-Higueras F, Sánchez-Alonso S, Baca-García E, Barrigón ML; Spanish Metacognition Study Group. Jumping to conclusions and suicidal behavior in depression and psychosis. J Psychiatr Res. 2021 May;137:514-520. doi: 10.1016/ j.jpsychires.2021.03.024. Epub 2021 Mar 25. PMID: 33812324.*
Publication	*Eva Frigola-Capell, René Morgan, Albert Nogué, Ingrid Thelen, Jordi Font, Begoña Gonzalvo, Pilar Oliveras, Eva Bacardí, Maria Dolors Malla, Alex Gimeno, Anna Pla, Domènech Serrano, Eduard Palomer, Glòria Trafach, Jose Luís Ignacio Sagredo, Margarita De Castro.... Towards a classification framework for patient safety incidents and adverse events for a mental health community-based model of service provision. Revista de Psiquiatría y Salud Mental. 2021. 10.1016/j.rpsm.2021.11.007*
Publication	*Campuzano, Oscar; Sarquella-Brugada, Georgia; Fernandez-Falgueras, Anna; et al; Brugada, Ramon. 2020. Reanalysis and reclassification of rare genetic variants associated with inherited arrhythmogenic syndromes EBioMedicine. Elsevier B.V.. 54. ISSN 23523964*
Publication	*Birulés I, López-Carrilero R, Cuadras D, Pousa E, Barrigón ML, Barajas A, Lorente-Rovira E, González- Higueras F, Grasa E, Ruiz-Delgado I, Cid J, de Apraiz A, Montserrat R, Pélaez T, Moritz S, The Spanish Metacognition Study Group, Ochoa S. Cognitive Insight in First-Episode Psychosis: Changes during Metacognitive Training. Journal of personalized medicine. Nov 27;10(4):253. 2020-11 PMID: 33260823PMC: PMC7711871 DOI: 10.3390/jpm10040253 Europe PubMed Central*

List of up to 5 most relevant previous projects or activities, connected to the subject of this proposal.

Name of Project or Activity	Short description (Max 500 characters)
REFINEMENT	*Proyecto REFINEMENT España (FUNDACIO PRIVADA INSTITUT D'INVESTIGACIO BIOMED DE GIRONA DR. JOSEP TRUETA). Desde 2016*
LINNEAUS EURO-PC	*Learning from international networks about errors and understanding safety in Primary Care (LINNEAUS EURO-PC) FP7-HEALTH-2007-B / Coordination and support action*
Psicosis biases	*Influencia del estilo de apego en la cognición social y sesgos cognitivos en personas con un primer episodio psicótico, esquizofrenia crónica y controles sanos/as. PERIS-Generalitat de Catalunya. Codi PIC-187-18 Codi CEIm 2019*

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work.

Name of infrastructure of equipment	Short description (Max 300 characters)

BIOBANK	*The IDIBGI Biobank is the support platform for research responsible for the management of human biological samples and associated data for research. This management includes collection, processing, storage, and transfer of samples to promote quality biomedical research.*
GENCARDIO DIAGNOSTICS	*Gencardio Diagnostics has developed different panels available for genetic diagnosis and has several collaborations with foundations and companies for the development of genetic panels for different diseases, their manufacture and commercialisation.*
Patient Safety Unit for Mental Health	*Multidisciplinary Inter-sectorial Patient Safety Unit for Mental Health. Knowledge based on quality improvement, implementation science and patient safety methodology applied in building capacity in patient safety culture in mental Health in Girona.*

Gender Equality Plan

Does the organization have a Gender Equality Plan (GEP) covering the elements listed below? (•) Yes ( ) No

Minimum process-related requirements (building blocks) for a GEP

- **Publication:** formal document published on the institution's website and signed by the top management
- **Dedicated resources:** commitment of human resources and gender expertise to implement it.
- **Data collection and monitoring:** sex/gender disaggregated data on personnel (and students for establishments concerned) and annual reporting based on indicators.
- **Training:** Awareness raising/trainings on gender equality and unconscious gender biases for staff and decision-makers.
- **Content-wise, recommended areas** to be **covered** and addressed via concrete measures and targets are:
    - work-life balance and organisational culture;
    - gender balance in leadership and decision-making;
    - gender equality in recruitment and career progression;
    - integration of the gender dimension into research and teaching content;
    - measures against gender-based violence including sexual harassment.

PIC	Legal name
967774433	*ISTANBUL MEDIPOL UNIVERSITESI*

Short name: IMU

Address

Street	ATATURK BULVARI 27 FAITH KASAPDEMIRHUN M
Town	ISTANBUL
Postcode	34083
Country	Turkey
Webpage	www.medipol.edu.tr

Specific Legal Statuses

Legal person	yes
Public body	no
Non-profit	yes
International organisation	no
Secondary or Higher education establishment	yes
Research organisation	yes

SME Data

Based on the below details from the Participant Registry the organisation is not an SME (small- and medium-sized enterprise) for the call.

SME self-declared status	07/07/2009 - no
SME self-assessment	unknown
SME validation	unknown

Departments carrying out the proposed work

Department 1

Department name: Technology Transfer Office Project Management Office

☐ not applicable

☐ Same as proposing organisation's address

Street: Ekinciler Caddesi, No: 19 Beykoz

Town: Istanbul

Postcode: 34810

Country: Turkey

Links with other participants

Type of link	Participant

Main contact person

This will be the person the EU services will contact concerning this proposal (e.g. for additional information, invitation to hearings, sending of evaluation results, convocation to start grant preparation). The data in blue is read-only. Details (name, first name and e-mail) of Main Contact persons should be edited in the step "Participants" of the submission wizard.

Title Mrs

Gender ◉ Woman ○ Man ○ Non Binary

First name* **Meltem**

Last name* **Simsek**

E-Mail* **meltem.simsek@medipol.edu.tr**

Position in org. EU project manager

Department ISTANBUL MEDIPOL UNIVERSITESI ☒ Same as organisation name

☒ Same as proposing organisation's address

Street ATATURK BULVARI 27 FAITH KASAPDEMIRHUN MAHALLESI

Town ISTANBUL

Post code 34083

Country Turkey

Website *Please enter website*

Phone *+xxx xxxxxxxxx*

Phone 2 *+xxx xxxxxxxxx*

Other contact persons

First Name	Last Name	E-mail	Phone
Ilker	Kose	ikose@medipol.edu.tr	+xxx xxxxxxxxx
Esra	Agrali	esraagrali@medipol.edu.tr	+xxx xxxxxxxxx

Researchers involved in the proposal

Title	First Name	Last Name	Gender	Nationality	E-mail	Career Stage	Role of researcher (in the project)	Reference Identifier	Type of identifier
Prof	Erdem	DEVECİ	Man	Turkey	erdem.deveci@medipol.edu.tr	Category A Top grade re	Leading	0000-0002-9661-8344	Orcid ID
Prof	Alperen	Kilic	Man	Turkey	alperenkilic88@hotmail.com	Category B Senior resea	Team member	0000-0003-2610-1830	Orcid ID
Mr	Burak	Amil	Man	Turkey	Burakamil13@gmail.com	Category D First stage r	Team member	0000-0003-0918-3395	Orcid ID
Mrs	Meltem	Şimşek	Woman	Turkey	Meltem.simsek@medipol.edu.tr		Team member		
Mrs	Esra	Ağralı	Woman	Turkey	esraagrali@medipol.edu.tr		Team member		
Mrs	Kubra	Yurduseven	Woman	Turkey	k.yurduseven@intract.com.tr		Team member		

Role of participating organisation in the project

Project management	☒
Communication, dissemination and engagement	☒
Provision of research and technology infrastructure	☐
Co-definition of research and market needs	☐
Civil society representative	☐
Policy maker or regulator, incl. standardisation body	☐
Research performer	☒
Technology developer	☐
Testing/validation of approaches and ideas	☒
Prototyping and demonstration	☐
IPR management incl. technology transfer	☐
Public procurer of results	☐
Private buyer of results	☐
Finance provider (public or private)	☐
Education and training	☐
Contributions from the social sciences or/and the humanities	☐
Other If yes, please specify: (Maximum number of characters allowed: 50)	☐

List of up to 5 publications, widely-used datasets, software, goods, services, or any other achievements relevant to the call content.

Type of achievement	Short description (Max 500 characters)
Publication	*Öztürk, A., Kiliç, A., Deveci, E., & Kirpinar, İ. (2016). Investigation of facial emotion recognition, alexithymia, and levels of anxiety and depression in patients with somatic symptoms and related disorders. Neuropsychiatric disease and treatment, 12, 1047–1053. https:// doi.org/10.2147/NDT.S106989*
Publication	*Elbay, R. Y., Görmez, A., Kılıç, A., & Avcı, S. H. (2021). Separation anxiety disorder among outpatients with major depressive disorder: Prevalence and clinical correlates. Comprehensive psychiatry, 105, 152219. https://doi.org/10.1016/j.comppsych.2020.152219*
Publication	*Kilic, A., Ozturk, A., Deveci, E., & Kirpinar, I. (2018). Development of hyperprolactinemia induced by the addition of Bupropion to Venlafaxine XR treatment. Bezmialem Science, 6, 150-152. DOI: 10.14235/bs.2018.1119*
Publication	*Antiparkinsonian and psychiatric drugs, Alperen Kiliç, 2021; November 17-20 2021; Royal Seginus Hotel, Antalya, 12th International Congress on Psychopharmacology & 8th International Symposium on Child and Adolescent Psychopharmacology. ISBN no: 978-605-70422-8-6*
Publication	*Microbiota, Cognition, Stress, Anxiety, Depression, Probiotics in Bipolar Mood Disorder and Schizophrenia, ed. A İ KİLCİ, R A OKYAY, A R ŞAHİN, Chapter Author: A Kılıç, Academician Publishing House, Ankara, 2019. ISBN: 9786052587300 (Microbiota, Cognition, Stress, Anxiety, Depression, Probiotics in Bipolar Mood Disorder and Schizophrenia, ed. A İ KİLCİ , R A OKYAY, A R ŞAHİN, Chapter Author: A Kılıç, Academician Publishing House, Ankara, 2019. ISBN: 9786052587300)*

List of up to 5 most relevant previous projects or activities, connected to the subject of this proposal.

Name of Project or Activity	Short description (Max 500 characters)
TUBITAK 1001	*TUBITAK 1001 Project, executive investigator, The project consists of steps such as designing the focused ultrasound treatment apparatus, determining real-time ultrasound wave dynamics, microscopically showing the necrosed brain tissue area of the sacrificed rat after applying high energy sonification & assessing whether it overlaps with the target tissue, forming an alcohol model in rats, sonification, following animals' alcohol-water consumption, & lastly analyzing the brain tissue of animals*
Investigation of the Effects of Nucleus Accumbense	*Scientific Research Project Supported by Higher Education Institutions, principle investigator, The project was designed in two stages. In the first stage, rats were divided into two groups: serum physiologic (SF) and morphine. Reinforcement and rewarding effects of morphine were assessed by using a 14-days Conditioned Place*
Preference (CPP) protocol	*Preference (CPP) protocol. At the second stage, morphine group (conditioned by the administration of morphine) was divided into two groups: SHAM group, which receive fake stimuli and US group which receive low intensity focused ultrasonographic stimulation. During the 10-day stimulation phase, SF group did not receive any stimulation and CPP procedure was being held simultaneously with SF injections during this phase.*
Scientific Research Project Supported	*Scientific Research Project Supported by Higher Education Institutions, principle investigator. A total of 37 patients (11 male and 26 female) aged between 18 and 65 years with at least 5 years of education who applied to the Dermatology Outpatient Clinic of the study hospital between study period; diagnosed with psoriasis by physical examination and histopathological evaluation were included in the project. The control group was formed from healthy individuals working for the hospital.*

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work.

Name of infrastructure of equipment	Short description (Max 300 characters)
Regenerative and Restorative Medicine Research	*REMER is organized to harbor multiple core facilities and labs with the highest technology available and has already started to attract many high profile researchers from all over the world.*
REMER	*We have a vision to cover all main areas of the regenerative medicine by encouraging formation of several topic-specific research groups led by prominent scientists.(http:// remer.medipol.edu.tr/)*
REMER	*REMER includes laboratories below as:* *1.Cell Culture and Solter Laboratory* *2.Molecular Biology and Histology Laboratory* *3.Electrophysiology Laboratory* *4.Proteomics Laboratory* *5.Advanced Microscopy Laboratory I* *6. Advanced Microscopy Laboratory II* *7. Advanced Microscopy Laboratory III*
REMER	*8. Advanced Microscopy Laboratory IV* *9.Optogenetic and Electrophysiology Laboratory* *10.Pharmacognosis Laboratory* *11.Pharmaceutical Chemistry Laboratory* *Visual Tour via https://sanaltur.medipol.edu.tr/remer.html*

Gender Equality Plan

Does the organization have a Gender Equality Plan (GEP) covering the elements listed below? (•) Yes ( ) No

Minimum process-related requirements (building blocks) for a GEP

- **Publication:** formal document published on the institution's website and signed by the top management
- **Dedicated resources:** commitment of human resources and gender expertise to implement it.
- **Data collection and monitoring:** sex/gender disaggregated data on personnel (and students for establishments concerned) and annual reporting based on indicators.
- **Training:** Awareness raising/trainings on gender equality and unconscious gender biases for staff and decision-makers.
- **Content-wise, recommended areas** to be **covered** and addressed via concrete measures and targets are:
    - work-life balance and organisational culture;
    - gender balance in leadership and decision-making;
    - gender equality in recruitment and career progression;
    - integration of the gender dimension into research and teaching content;
    - measures against gender-based violence including sexual harassment.

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3 - Budget

No.	Name of beneficiary	Country	Role	Personnel costs/€	Subcontracting costs/€	Purchase costs - Travel and substistence /€	Purchase costs - Equipment/€	Purchase costs - Other goods, works and services/€	Internally invoiced goods and services/€ (Unit costs-usual accounting practices)	Indirect costs/€	Total eligible costs	Funding rate	Maximum EU contribution to eligible costs	Requested EU contribution to eligible costs/€	Max grant amount	Income generated by the action	Financial contributions	Own resources	Total estimated income
1	Fondazione Ebris	IT	Coordinator	855,000	0	45,000	22,000	370,500	0	323125.00	1615625.00	100	1615625.00	1,615,625	1615625.00	0	0	0	1615625.00
2	Ceinge Biotecnologie Avanzate Scarl	IT	Partner	207,000	0	20,000	0	463,000	0	172500.00	862500.00	100	862500.00	862,500	862500.00	0	0	0	862500.00
3	Fundacio Eurecat	ES	Partner	344,400	0	20,000	0	334,000	0	174600.00	873000.00	100	873000.00	873,000	873000.00	0	0	0	873000.00
4	Perseus Biomics	BE	Partner	170,500	0	20,000	0	365,000	0	138875.00	694375.00	100	694375.00	694,375	694375.00	0	0	0	694375.00
5	Artificial Intelligence Expert Srl	RO	Partner	710,000	0	20,000	0	39,000	0	192250.00	961250.00	100	961250.00	961,250	961250.00	0	0	0	961250.00
6	Mama Health Technologies Gmbh	DE	Partner	442,000	0	20,000	0	127,000	0	147250.00	736250.00	100	736250.00	736,250	736250.00	0	0	0	736250.00
7	Protobios Ou	EE	Partner	297,000	0	20,000	0	118,000	0	108750.00	543750.00	100	543750.00	543,750	543750.00	0	0	0	543750.00
8	Cephalgo	FR	Partner	312,000	0	20,000	0	213,100	0	136275.00	681375.00	100	681375.00	681,375	681375.00	0	0	0	681375.00
9	Biokeralty Research Institute Aie	ES	Partner	162,000	0	20,000	0	20,000	0	50500.00	252500.00	100	252500.00	252,500	252500.00	0	0	0	252500.00

10	Fundación Universitaria Sanitas	CO	Partner	243,000	0	20,000	0	36,975	0	74993.75	374968.75	100	374969.00	374,969	374969.00	0	0	0	374969.00
11	Universita Degli Studi Di Siena	IT	Partner	522,000	0	31,250	0	49,975	0	150806.25	754031.25	100	754031.00	754,031	754031.00	0	0	0	754031.00
12	Stichting Universitaire En Algemene Kinder - En Jeugdpsychiatrie Noord-nederland	NL	Partner	426,000	0	20,000	0	36,000	0	120500.00	602500.00	100	602500.00	602,500	602500.00	0	0	0	602500.00
13	Fundacio Institut D'investigacio Biomedica De Girona Doctor Josep Trueta	ES	Partner	364,500	0	20,000	0	129,000	0	128375.00	641875.00	100	641875.00	641,875	641875.00	0	0	0	641875.00
14	Istanbul Medipol Universitesi	TR	Partner	266,000	0	20,000	0	36,875	0	80718.75	403593.75	100	403594.00	403,594	403594.00	0			403594.00
			TOTAL	5,321,400	0	316,250	22,000	2,338,425	0	1999518.75	9997593.75		9997594.00	9,997,594	9997594.00	0	0	0	9997594.00

4 - Ethics & security

Ethics Issues Table

1. Human Embryonic Stem Cells and Human Embryos			Page
Does this activity involve Human Embryonic Stem Cells (hESCs)?	○ Yes	◉ No	
Does this activity involve the use of human embryos?	○ Yes	◉ No	
2. Humans			**Page**
Does this activity involve human participants?	◉ Yes	○ No	9
Are they volunteers for non medical studies (e.g. social or human sciences research)?	○ Yes	◉ No	
Are they healthy volunteers for medical studies?	○ Yes	◉ No	
Are they patients for medical studies?	◉ Yes	○ No	9
Are they potentially vulnerable individuals or groups?	○ Yes	◉ No	
Are they children/minors?	◉ Yes	○ No	9
Are they other persons unable to give informed consent?	○ Yes	◉ No	
Does this activity involve interventions (physical also including imaging technology, behavioural treatments, etc.) on the study participants?	○ Yes	◉ No	
Does this activity involve conducting a clinical study as defined by the Clinical Trial Regulation (EU 536/2014)? (using pharmaceuticals, biologicals, radiopharmaceuticals, or advanced therapy medicinal products)	◉ Yes	○ No	9
Is it a clinical trial?	○ Yes	◉ No	
Is it a low-intervention clinical trial?	◉ Yes	○ No	9
3. Human Cells / Tissues (not covered by section 1)			**Page**
Does this activity involve the use of human cells or tissues?	○ Yes	◉ No	
4. Personal Data			**Page**
Does this activity involve processing of personal data?	◉ Yes	○ No	9
Does it involve the processing of special categories of personal data (e.g.: genetic, biometric and health data, sexual lifestyle, ethnicity, political opinion, religious or philosophical beliefs)?	◉ Yes	○ No	9
Does it involve processing of genetic, biometric or health data?	◉ Yes	○ No	9
Does it involve profiling, systematic monitoring of individuals, or processing of large scale of special categories of data or intrusive methods of data processing (such as, surveillance, geolocation tracking etc.)?	○ Yes	◉ No	
Does this activity involve further processing of previously collected personal data (including use of preexisting data sets or sources, merging existing data sets)?	○ Yes	◉ No	
Is it planned to export personal data from the EU to non-EU countries? Specify the type of personal data and countries involved	○ Yes	◉ No	
Is it planned to import personal data from non-EU countries into the EU or from a non-EU country to another non-EU country? Specify the type of personal data and countries involved	◉ Yes	○ No	9

Colombia, Turkey
Importation of health data

Does this activity involve the processing of personal data related to criminal convictions or offences?	○ Yes	◉ No	

5. Animals			Page
Does this activity involve animals?	○ Yes	◉ No	

6. Non-EU Countries			Page
Will some of the activities be carried out in non-EU countries?	◉ Yes	○ No	9

Colombia, Turkey

In case non-EU countries are involved, do the activities undertaken in these countries raise potential ethics issues?	○ Yes	◉ No	
It is planned to use local resources (e.g. animal and/or human tissue samples, genetic material, live animals, human remains, materials of historical value, endangered fauna or flora samples, etc.)?	○ Yes	◉ No	
Is it planned to import any material (other than data) from non-EU countries into the EU or from a non-EU country to another non-EU country? For data imports, see section 4.	◉ Yes	○ No	9

Colombia, Turkey
Patient samples

Is it planned to export any material (other than data) from the EU to non-EU countries? For data exports, see section 4.	○ Yes	◉ No	
Does this activity involve low and/or lower middle income countries, (if yes, detail the benefit-sharing actions planned in the self-assessment)	◉ Yes	○ No	9
Could the situation in the country put the individuals taking part in the activity at risk?	○ Yes	◉ No	

7. Environment, Health and Safety			Page
Does this activity involve the use of substances or processes that may cause harm to the environment, to animals or plants.(during the implementation of the activity or further to the use of the results, as a possible impact) ?	○ Yes	◉ No	
Does this activity deal with endangered fauna and/or flora / protected areas?	○ Yes	◉ No	
Does this activity involve the use of substances or processes that may cause harm to humans, including those performing the activity.(during the implementation of the activity or further to the use of the results, as a possible impact) ?	○ Yes	◉ No	

8. Artificial Intelligence			Page
Does this activity involve the development, deployment and/or use of Artificial Intelligence? (if yes, detail in the self-assessment whether that could raise ethical concerns related to human rights and values and detail how this will be addressed).	◉ Yes	○ No	9

9. Other Ethics Issues	Page

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Are there any other ethics issues that should be taken into consideration?	◯ Yes	◉ No	

I confirm that I have taken into account all ethics issues above and that, if any ethics issues apply, I will complete the ethics self-assessment as described in the guidelines How to Complete your Ethics Self-Assessment ☒

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Ethics Self-Assessment

Ethical dimension of the objectives, methodology and likely impact

Social and clinical value: Clinical investigation intends to answer specific key objectives relative to the optimisation of the anti-depressant efficacy for MDD patients. No new drugs will be tested in this trial and the collection of the samples is done according to very standard procedures (blood, stool, saliva). With positive outcomes, the benefits from the study will be immense not only for the enrolled patients but also for the MDD population.
Informed consent: for research on human subjects to be ethical, individuals should make their own decision about whether they want to participate or continue participating in research. This is done through a process of informed consent in which individuals (1) are accurately informed of the purpose, methods, risks, benefits, and alternatives to the research, (2) understand this information and how it relates to their own clinical situation or interests, and (3) make a voluntary decision about whether to participate.
We will collect stool, blood and saliva samples up to 5 times over the study duration. Patient follow-up is set up at 24 months, with face to face visits. Patient samples are stored at -80 degrees up to further analysis. European and non-European clinical sites will ship patient samples to EBRIS for biobanking. A variety of analysis is performed on patient samples to establish specific MDD patterns. Patient data are pseudonymised since their enrolment in the study. Researchers cannot link results to a specific patient. For publication, the geography will be indicated for epidemiologic purposes.
Scientific validity: clinical trials are designed to get an understandable answer to the research question. This includes considering whether the question researchers are asking is answerable, whether the research methods are valid and feasible, whether the study is designed with a clear scientific objective and is using accepted principles, methods and reliable practices. It is also important that statistical plans be of sufficient power to definitively test the objective.
Medical research can place participants at risk of harm for the benefit of others thus, clinical trials have the potential to exploit patient volunteers. The purpose of ethical review is both to protect patient volunteers and to preserve the integrity of the science. The guidance for ethical considerations came about in the 20th Century following situations such as the Second World War and thalidomide disaster.
The use of AI in patient analysis may raise significant concerns. We will ensure model reliability, fairness, explainability and data protection as detailed in lenght in the proposal (p13).
The integration of LMIC (Columbia and Turkey) is bringing an considerable added value in our proposal. As we investigate the impact of the microbiome on mental health, the assessment of the environment is key. Integrating such different diet and life style will ensure that data consider a verity of patient in the development of the digital solution.

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Compliance with ethical principles and relevant legislations

Some of the influential codes of ethics and regulations that guide ethical clinical research include Nuremberg Code (1947), Declaration of Helsinki (1964, amended in 1975, 1983, 1989, 1996, 2000, 2002, 2004, 2008, 2013), Belmont Report (1979), CIOMS (1982), ICH GCP (1997), Regulation EU No 536/2014
Using these sources of guidance, the main principles have been described as guiding the conduct of ethical research:
Fair subject selection: the basis for recruiting and enrolling individuals should be the scientific goals of the clinical trial and not vulnerability, privilege, or other factors unrelated to the purposes of the study. Consistent with the scientific purpose, people should be chosen in a way that minimizes risks and enhances benefits to individuals and society. Specific groups or individuals (for example, women or children) should not be excluded from the opportunity to participate in research without a good scientific reason or a particular susceptibility to risk (for example pregnancy). Pre-clinical data are sufficient to integrate pregnant / lactating women in our adult clinical trial. We will discuss with EMA and national competent authorities on the appropriate timing to integrate them in the trial.
Favourable risk-benefit ratio: uncertainty about the degree of risks and benefits associated with a drug, device, or procedure being tested is inherent in clinical research — otherwise there would be little point to doing the research. Risks can be physical (death, disability, infection), psychological (depression, anxiety), economic (job loss), or social (for example, discrimination or stigma from participating in a certain trial). Has everything been done to minimize the risks and inconvenience to research subjects, to maximize the potential benefits, and to determine that the potential benefits to individuals and society are proportionate to, or outweigh, the risks? Research volunteers often receive some health services and benefits in the course of participating, yet the purpose of clinical research is not to provide health services.
Respect for potential and enrolled subjects: individuals should be treated with respect from the time they are approached for possible participation—even if they refuse enrolment in a study throughout their participation and after their participation ends. This includes the respect of their privacy and confidential information and the respect of their right to change their mind, to decide that the research does not match their interests, and to withdraw without penalty. Patients will be informed of any new information that

might emerge in the course of research, which might change their assessment of the risks and benefits of participating. We will monitor their welfare and, if they experience adverse reactions, untoward events, or changes in clinical status, ensuring appropriate treatment and, when necessary, removal from the study. Finally, they will have access to research results.
All medical research involving human subjects must be approved by an independent ethics committee before the research can start. The committee protects the rights and interests of the people who will be in the trial based on the above criteria. The committees are often based at local hospitals and are formed of local people, such as healthcare professionals, patients, lawyers and members of the public. The ethics committees have to include members who are not healthcare professionals. The committees are independent both of the researchers whose work they are reviewing and those who pay for the research. Until a research ethics committee approves a clinical trial, researchers cannot ask any participants to join it.

AI modules: We will follow the data governance concepts outlined in the GDPR Recitals 71, Article 4 and Articles 13 and 14, and 22

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Security issues table

1. EU Classified Information (EUCI)[2]		Page
Does this activity involve information and/or materials requiring protection against unauthorised disclosure (EUCI)?	○ Yes ◉ No	
Does this activity involve non-EU countries?	○ Yes ◉ No	
2. Misuse		**Page**
Does this activity have the potential for misuse of results?	○ Yes ◉ No	
3. Other Security Issues		**Page**
Does this activity involve information and/or materials subject to national security restrictions? If yes, please specify: (Maximum number of characters allowed: 1000)	○ Yes ◉ No	
Are there any other security issues that should be taken into consideration? If yes, please specify: (Maximum number of characters allowed: 1000)	○ Yes ◉ No	

[2]According to the Commission Decision (EU, Euratom) 2015/444 of 13 March 2015 on the security rules for protecting EU classified information, "European Union classified information (EUCI) means any information or material designated by an EU security classification, the unauthorised disclosure of which could cause varying degrees of prejudice to the interests of the European Union or of one or more of the Member States".

[3]Classified background information is information that is already classified by a country and/or international organisation and/or the EU and is going to be used by the project. In this case, the project must have in advance the authorisation from the originator of the classified information, which is the entity (EU institution, EU Member State, third state or international organisation) under whose authority the classified information has been generated.

[4]EU classified foreground information is information (documents/deliverables/materials) planned to be generated by the project and that needs to be protected from unauthorised disclosure. The originator of the EUCI generated by the project is the European Commission.

5 - Other questions

Essential information to be provided for proposals including clinical Trials / studies / investigations

Clinical study means, for the purpose of this document, any systematic prospective or retrospective collection and analysis of health data obtained from individual patients or healthy persons in order to address scientific questions related to the understanding, prevention, diagnosis, monitoring or treatment of a disease, mental illness, or physical condition. It includes but it is not limited to clinical studies as defined by Regulation 536/2014 (on medicinal products), clinical investigation and clinical evaluation as defined by Regulation 2017/745 (on medical devices), performance study and performance evaluation as defined by Regulation 2017/746 (on in vitro diagnostic medical devices).

Are clinical studies / trials / investigations included in the work plan of this project? (●) Yes ( ) No

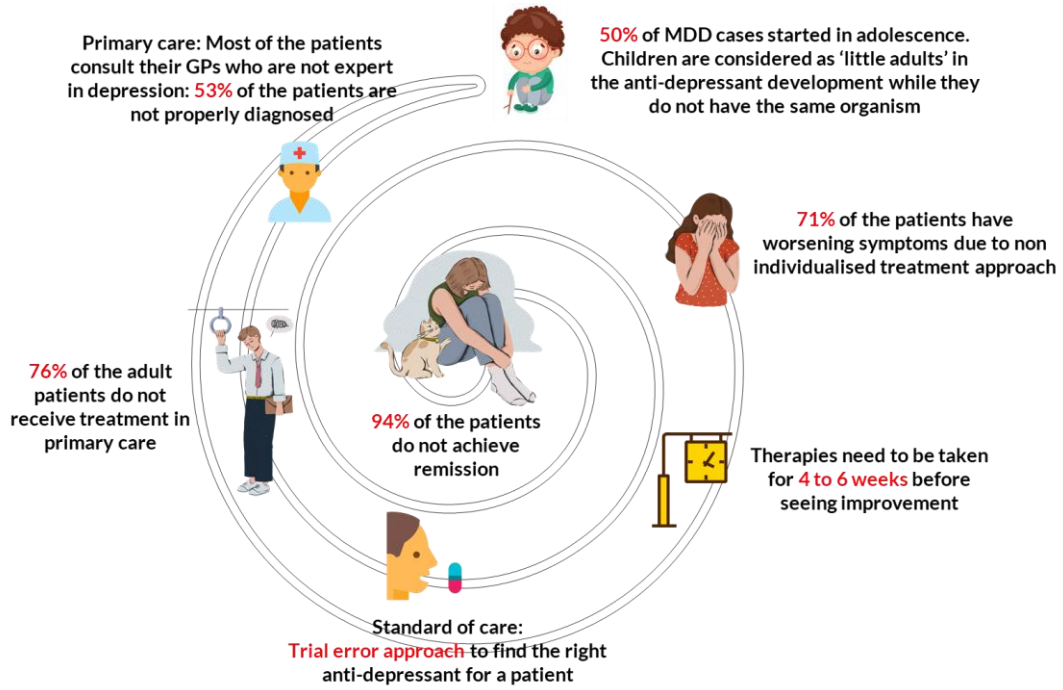
Please upload the dedicated annex 'Essential information for clinical studies / trials / investigations' (a Word template is provided under 'download templates' in the up-load section for Part B and Annexes).

This document should include the relevant information of each clinical study / trial / investigation included in the work plan of this project.

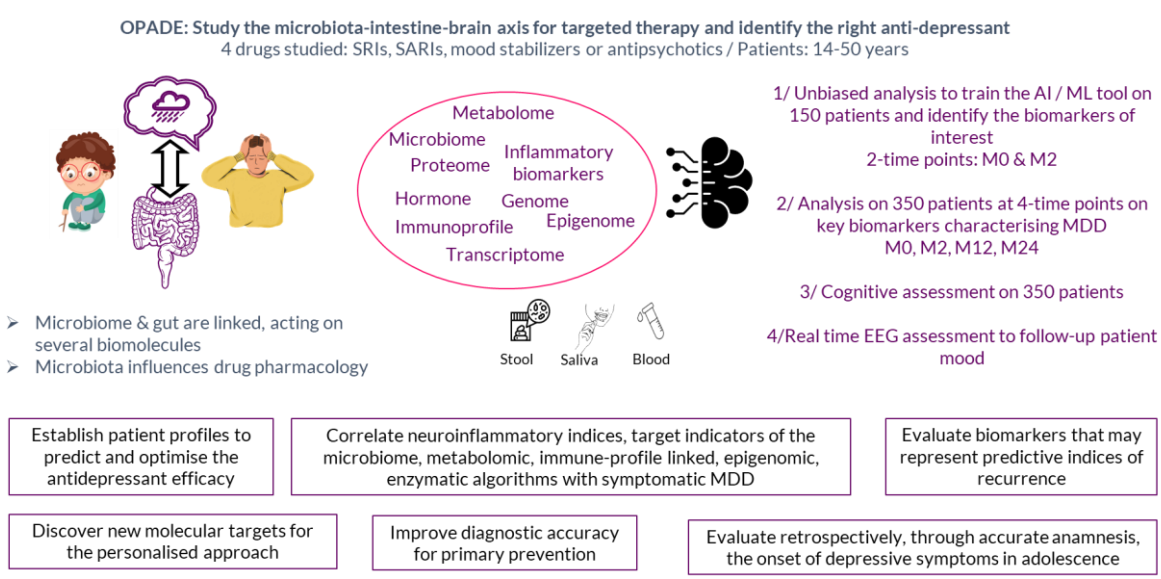
Please give a short title, an acronym or a unique identifier to each clinical study / trial / investigation, to be used as a reference/ identifier in the other parts of the proposal.
OPADE

OPADE: Optimise and predict antidepressant efficacy for patients with major depressive disorders using multi-omics analysis and AI-predictive tool

PROBLEM



PROJECT IMPACT



#	Organization	Short name	Type	Country
1	European Biomedical Research Institute Salerno	EBRIS	Academic	IT
2	Ceinge Biotecnologie Avanzate SCRL	CEINGE	Academic	IT
3	Eurecat	EUT	Academic	SP
4	Perseus Biomics	PBIO	Private	BE
5	Artificial intelligence experts	AIE	Private	RO
6	MamaHealth	MMH	Private	DE
7	Probios	PRO	Private	EE
8	Cephalgo	CEP	Private	FR
9	Biokeralty	BIOK	Private	SP
10	Fundation Universitaria Sanitas	FUS	Clinical	CO
11	Università di Siena	UNISA	Clinical	IT
12	Accare (University Medical Center Groningen)	ACC	Clinical	NL
13	Institut d'Investigació Biomèdica de Girona Dr. Josep Trueta	IDIBGI	Clinical	SP
14	Instanbul Medipol Universitiesi	MED	Clinical	TR

Abstract

280M of people worldwide suffer from major depressive disorders (MDD). Although there is 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 fully benefit from the current therapeutic journey.
OPADE's objective is to identify key biomarkers that support the decision-making process of the healthcare providers through the development and commercialisation of an AI (artificial intelligence) / ML (machine learning) -predictive tool.
The project focuses on the gut–brain-axis which plays a major role in MDD. Through clinical investigations, the consortium partners will study the combination between genetics, epigenetics, microbiome and inflammatory networks to:

- Establish patient profiles to predict & 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
- 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 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 to ensure patient commitment and to translate patient stories into data.

Terminology

Acr.	Explanation	Acr.	Explanation
AI	Artificial intelligence	MGB	Microbiota-Intestine-Brain
EEG	Electro encephalography	MVA	Mimotope variation analysis
MAP	Metagenomic abundance profiling	SARI	Serotonin antagonist and reuptake inhibitor
MDD	Major depressive disorder	SSRI	Selective serotonin reuptake inhibitor
ML	Machine learning		

1. Excellence

Major depression disorders (MDD) expected leading cause of disability by 2030

From addiction to dementia, almost 1bn people worldwide suffer from a mental disorder. Major depressive disorders (MDDs) are the most prevalent mental health conditions. MDD is not just usual mood fluctuations and short-lived emotional responses to challenges in everyday life. MDD affects the individual in his/her entire life, at work, at school and within the family. Lost productivity resulting from anxiety and MDD costs the global economy €1tn every year. In 2021, WHO estimates that 280M people worldwide suffer from MDD, *i.e.* 3.8% of the population.

MDD and COVID-19 crisis: On average 4 in 10 adults over 18 reported anxiety or depression since the pandemic started[1]. Loneliness, younger age, female sex and low income impact this number. The number of sick leaves jumped by 30% during early 2021, with 19% of these reasons being depression or anxiety. The pandemic also led to an exacerbated mental health disorder prevalence among the healthcare directly exposed to the crisis management resulting from the fear to get infected, of being infected and being separated from their families. 26% reported depression, with a highest prevalence for workers aged between 29 and 35 years old. A UNICEF study indicates that 27% of people aged between 13 and 29 experienced anxiety and 15% reported depression. The crisis largely demonstrated the sex imbalance with women reporting more depression than men.

MDD and war in Ukraine: The Russian invasion of Ukraine on Feb. 24, 2022 already caused the displacement of millions of Ukrainians to escape their country; if staying in the country, people are hiding in bomb shelters and basements. Experts are raising a warning flag on the mental health of civilians who are not prepared for war. In particular, children are the most exposed. In addition to being directly traumatised by the armed conflict, the risk of mental instability of their parents increases their own risk to develop anxiety or depression. Also the youngest babies are concerned. A mum who does not give back a smile signals danger to the baby and may hurt its development. Finally, such a conflict confirms the sex imbalance in mental health. While men cannot leave the country and are at risk of getting killed, women are leaving with the risk of leaving their husbands, sons, and fathers and facing bereavement.

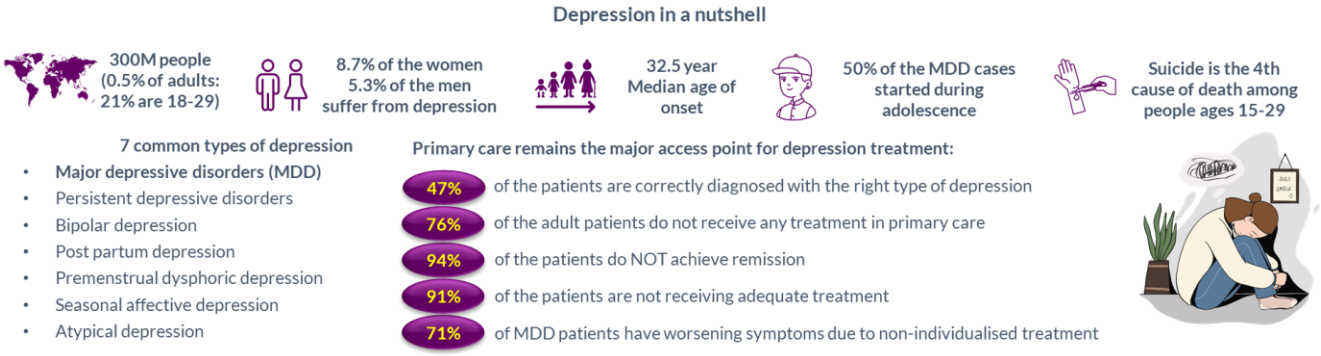


Figure 1. Depression general presentation and statistics[2]

Major depression disorder treatment options

Psychiatrists have a long list of anti-depressants that they can prescribe to their patients for the acute and prophylactic treatment of depressed patients. It includes monoamine oxidase inhibitor (MAOIS), tricyclic antidepressant (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitor (SSRIs). The most recent class of anti-depressants (SSRI, SNRI) seems to have a longer-term effect than older molecules (TCA).

But because of the lack of clear guidelines and validated tools, general practitioners (GPs) and psychiatrists run a trial-error approach to find the right molecule for a specific patient. Existing guidelines recommend that initial treatment should be tried for a long period; on average, it takes at least 4 weeks to achieve response and 6 weeks to remission, but remission can take more than 12 weeks and is scarcely reached with the first drug tested.

As a consequence, almost 94% of patients do not recover following treatment with their first antidepressant and 20% of these patients do not respond to any intervention[3]. 42% of the patients stop treatment within the first 30 days, remaining out of the care pathway.

Personalised medicine to predict and optimize treatment efficacy – *State of the art*

Personalized medicine is key to optimising patient treatment and to increasing the chance of a full return to pre-morbid levels of functioning[4]. It is a challenge for healthcare practice in terms of basing medical decisions and treatments tailored to the single individual. Ideally, accurate diagnoses and patient-based therapeutic approaches can be provided during all phases of the disease, including prevention, diagnosis, prognosis, treatment, and follow-up.

To boost treatment benefits for patients with MDD, there is an urgent need to clearly understand the pathogenetic mechanisms of mood disorders. Even if a broad range of studies has attempted to investigate the interplay of psychological factors with environmental risk factors and biological

[1] *The global prevalence of depression among health workers during the COVID-19 pandemic, J Aff Dis R.; Rezaei et al., 2022*
[2] *The depression treatment cascade in primary care. Curr Psychiatry Rep, Pence et al., 2013,*
[3] *Biomarkers predicting antidepressant treatment response: how can we advance the field? Dis Markers. Lavermaier et al, 2013*
[4] *Pharmacological treatment of unipolar depressive disorders: Summary of WFSBP guidelines, Int J Psychiatry Clin Pract, Bauer et al., 2017*

mechanisms, the pathways that contribute to MDD onset remain far from elucidated. This lack of progress is partly attributed to the complexity and clinical heterogeneity of depression, in association with the analytical inconsistency of the literature. Current approached fail to identify biomarkers with sufficiently proven specificity, sensitivity and reproducibility.

A biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, and / or pathophysiological or pharmacological responses to a therapeutic intervention. Biomarkers could index the biological processes associated with a disease (diagnostic biomarkers), with the risk of developing a disease, or with the response to treatment or the outcome of a disease (predictive biomarkers). In psychiatry, biomarker research has proven to be more complex than in other medical disciplines[5]. For example, it is still debated whether mental disorders should be conceptualized as discrete entities (categorical approach) or as phenomena along a continuum of severity (dimensional approach). **As a consequence, the psychiatry field lacks behind other disciplines such as cancer or cardiovascular diseases: A very limited number of biomarkers have been identified as involved in MDD. In 2018, experts reported that almost no biomarkers were available in psychiatry. The discipline is slowly moving while mental health is now recognised as a major societal issue.**

Circular RNAs, abundantly expressed in the brain, have gained attention as promising biomarkers to inform MDD diagnosis and prognosis. The results of the clinical study conducted on 53 patients highlight that circMBNL1 may be a potential biomarker for diagnosis and circFKBP8 to assess treatment efficacy[6].

Early in 2022, a research group published that the heterotrimeric G protein, Gsalpha – a peripheral biomarker, may indicate the antidepressant efficacy for patients with MDD[7]. The study enrolled 19 patients and will need further investigations to reach conclusive results.

Recent findings suggest that the use of machine learning (ML) algorithms including genetic, clinical and demographic biomarkers improves accuracy in antidepressant prescription[8]. First in kind, Predictix, the application developed by Taliaz Health (Israel), drafted the way of using biological biomarkers and AI (Artificial Intelligence)-powered to identify the right treatment in MDD. Predictix, validated on 530 patients for 12 weeks, integrates genetic, clinical and demographic features to develop a predictive algorithm model for citalopram, sertraline and venlafaxine treatments. The algorithm demonstrates its capabilities of selecting a suitable antidepressant for an individual patient with an average balanced accuracy of 70.1%. However, their algorithm created predictions only for three medications, whereas clinicians have more therapeutic choices and their data did not include information to detect metabolizer phenotypes' inference. In addition, the clinical study did not include paediatric patients considering them as 'small adults'.

Besides the molecular biomarkers, physicians lack tools to monitor patient behaviour on a day-to-day basis. Psychiatrists are demanding reliable tool to track patients remotely to improve mental health in a efficient manner.

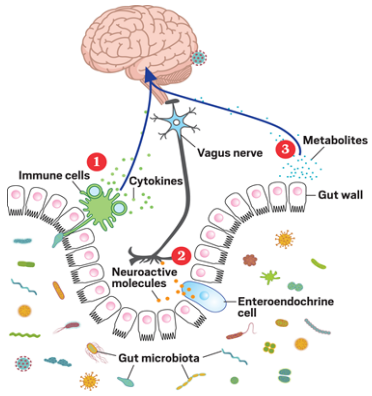
MDD in teenagers and young adults – Existing clinical guidelines do not answer the clinical need

MDD prevalence varies by age. US CDC numbers show that the percentage of adults who experienced any symptoms of depression was highest in the 18-29 population (21%), followed by those aged 45-64 (18.4%) and 65 and over (18.6%) and lastly, by people between 30-44 (16.8%). Over 700,000 people commit suicide every year – Suicide is the 4th leading cause of death in 15-29-years-olds. **MDD first occur during adolescence in nearly 50% of cases**, and the prevalence in this population is 5%, with a high risk of recurrence and chronicity across the lifespan[9]. Pre-adolescent rates of MDD are substantially lower, indicating that puberty onset is associated with the prevalence increase.

The use of the same diagnostic criteria in adults, children and adolescents suggests that the disorder is independent of age. However, there are important etiological differences between adolescent and adult disorders in terms of treatment response and genetic substrate. Evidence for the efficacy of antidepressants in treating adolescents is poorer than in adult depression; SSRs and tricyclic antidepressants show lower treatment effects than adults. Taken together, these features of depressive disorder clarify the need for early and effective intervention to treat adolescent depression.

[5] *The search for imaging biomarkers in psychiatric disorders*, Nat Med, Abi-Dargham & Horga, 2016
[6] *Potential clinical value of circular RNAs as peripheral biomarkers for the diagnosis and treatment of MDD*, Shi et al., The Lancet, 2021
[7] *A novel peripheral biomarker for depression and antidepressant response*, Molecular psychiatry, Targum et al., 2022
[8] *Optimizing prediction of response to antidepressant medications using ML & integrated genetic, clinical&demographic data*, Trans Psy, Taliaz et al., 2021
[9] *Understanding suicide: Focusing on its mechanisms through a lithium lens*, J. Affective Disorders, Malhi et al., 2018

The Microbiota-Intestine-Brain (MGB)



Microbiota-intestine-brain (MGB)

1. Microbes interact with immune cells in the gut, prompting the cells to make cytokines that circulate from the blood to the brain.
2. Microbes interact with gut cells called enteroendocrine cells that produce neuroactive molecules and peptides. These molecules interact with the vagus nerve, which sends signals to the brain.
3. Microbes in the gut produce neurotransmitters and metabolites like butyrate. These circulate to the brain, where some of them are small enough to cross the blood-brain barrier, and others alter cell activity at the barrier itself.

Figure 2. MGB advanced mechanism of action (Montiel-Castro et al., 2013)

Very recent findings (April 2022) evidence direct talks between the gut and the brain: The NOD2 receptor, expressed in different brain areas, has a modified activity in presence of muropeptides (derived compounds from the microbiome) and modulates the appetite in mice[10]. Increasing number of experimental and epidemiological findings suggest that the imbalanced gut microbiota – said in *dysbiosis* – is responsible for significant immunologic, neuronal and endocrine changes. **The microbiota-intestine-brain (MGB) axis is bi-directional: the gut affects the brain; the brain affects the gut**; using different signalling pathways such as the vagus nerve, the immune system and bacterial metabolites[11]. Dysbiosis dysregulates these pathways that lead to altered permeability of the blood-brain-barrier (BBB) and neuroinflammation. Piece of evidences suggest that patients with Alzheimer's and Parkinson's diseases, anxiety and depressive disorders are significantly impacted by dysbiosis. **About 60% of anxiety and depression patients report intestinal function disturbance such as irritable bowel syndrome**. The MGB axis exerts its effects through immune system activation (e.g., inflammatory cytokines and chemokines), neurotransmitter production (e.g., serotonin, gamma-aminobutyric acid [GABA] and glutamate) and through its metabolites (short-chain fatty acids (SCFA) and key dietary amino acids, such as tryptophan (TRP), while also exerting neuroendocrine functions.

Besides influencing specific brain functions, there are now growing proofs that the gut microbiome may also influence the efficacy of several drugs[12], including antidepressants (Walsh et al., 2018). Therefore, to implement personalised medicine and validate specific biomarkers for population stratification and prediction of drug efficacy, establishing the composition and function of the gut microbiome is becoming a key asset.

The Epigenetic and genetic signatures as predictors

Microbiome alteration and inflammatory mechanisms may in turn influence epigenetic patterns and vice versa. Thus, in this scenario epigenetics may represent a key actor and a link between different factors influencing the response and efficacy of several drugs in patients with MDD. Epigenetic profiles, are actively over-written on genomic sequence and dynamically determine the individual cell gene expression program without altering the underlying DNA sequence. DNA methylation represents an ideal biomarker to investigate, in both directions, how epigenetic profiles may associate with MDD risk and how environmental factors, including drug treatments, may have long-lasting effects on DNA activity programs. Moreover, the availability of reliable and affordable high-throughput array technologies makes it relatively easy to identify changes in DNA methylation at almost 1M locations along the genome in a single shot. Specific DNA methylation signatures have been recently proposed for evaluation of MDD risk and prediction of drug response in patients with MDD. Most studies suffered from small sample size or cell heterogeneity or missing cross analyses with additional biomarkers. Despite these limitations, different genes were described of which their methylation status was associated with the response to different drugs. The

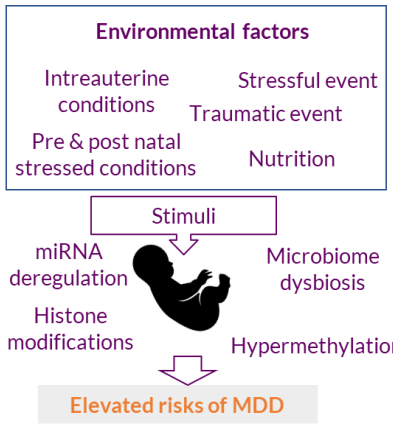


Figure 3. Environmental factors increase the risk of MDD since the earliest age (adapted from Saavedra etal., Int J Mol Sci, 2016)

[10] Bacterial sensing via neuronal Nod2 regulates appetite and body temperature, Gabanyi et al., Science, 2022
[11] The Gut-brain-axis: How microbiota and host inflammasome influence brain Physiology and pathology, Rutsch at al., Frontiers in Immunology, 2020
[12] Gut microbiome interactions with drug metabolism, efficacy, and toxicity, Wilson et al., Translational research, 2017

majority of these genes were strictly involved in neurotransmission. Some evidence demonstrated that DNA methylation signatures may help in predicting response to different MDD therapies. For instance, specific methylation levels found at certain CpG sites at BDNF, HTR1A and HTR1B, IL11 and IL6 genes were associated with antidepressant response.

Pharmacogenetics and long QT phenotype

Most MDD treatment (anti-depressants but also anti-psychotics) are metabolized by the polymorphic CYP2C19 and CYP2D6 enzymes. Both are highly polymorphic with known allelic variants and subvariants differing significantly among ethnic groups. The most commonly reported are categorized according to their active alleles into normal (NM), poor (PM), intermediate (IM) and ultrarapid (UM) metabolizers. This enzymatic activity determines the levels in plasma of drugs which have been found higher in PM and IM causing higher exposure to adverse drug reactions (ADR) for instance in risperidone, citalopram and escitalopram, aripiprazole, sertraline, venlafaxine among others. In addition, recent studies have found that those in the PM and UM categories are more prone to risperidone and escitalopram treatment failure, which was quantified as an increase in the incidence of switching to an alternative therapy within 1 year. On the other hand, those in the UM category most often show lower levels of response, due to faster drug metabolism.

Age, sex and ethnicity need to be considered when genotyping. Significant differences in allele proportions are observed among ethnically diverse populations. For instance, while European and African population have a similar proportion on CYP2C19, differences between them are found for CYP2D6. Gender may also have an impact on genotype profile. Sex differences have been reported for the pharmacokinetics of neuropsychopharmacological drugs, most likely due to effects of female sex hormones on the pharmacokinetic processes of absorption, distribution, metabolism and excretion. Regarding age, it is still not determined if enzymes decrease with age. Scarce researches have addressed the pharmacokinetics of antidepressants in children. Nevertheless, case studies or cohorts with small samples have identified a potential effect of allelic variants in CYP2D6 and CYP2C9 on therapeutic plasma levels and Adverse Drug Reactions.

How the enzymatic activity contributes to cardiovascular (CVD) risk, considering age, sex and ethnicity is still to be elucidated. It is well known that CVD risk and CVD-related deaths is higher in people taking MDD treatments than in the general population. This risk is increased by poor lifestyle and drug adverse effects. Patients with MDD who are stable under medication have higher prevalence of metabolic syndrome (MetS), which involves weight gain, abdominal obesity, elevated blood pressure, glucose intolerance and dyslipidemia. In addition, the use of first and second generation antipsychotics, is associated with a prolongation of the QT interval on the electrocardiogram, which may cause ventricular arrhythmias and sudden cardiac death. This has been observed to be dose-dependent; thus, tied to genetically determined drug pharmacokinetics. On the other, drug metabolism increases individuals' exposure in their risk of cardiovascular side effects, particularly in PM profile due to increased blood concentrations of the medication. Children, adolescents and the elderly are more likely to experience adverse events, or experience them more severely. While young are more prone to weight gain, elderly are to anticholinergic effects and orthostatic hypotension (falls). Nevertheless, the contribution of enzymes on age and adverse events is still to be elucidated, as well as how the gut genomics correlates with the enzymatic profiles. Selection of anti-depressant medication is usually done according to side effects and patients' preferences by trial and error. Hereby, treatment is initiated with the lowest effective dose until the therapeutic dosage is acquired with minimal side effects.

Based on these different shortcomings, OPADE consortium has determined a clinical need in identifying relevant molecular and non-molecular biomarkers to optimize the prescription of the treatments to patients who suffer from depression. The combination between epigenetics, microbiome and inflammatory network promise to robustly predict the drug response in these patients. Our project can contribute to personalized treatments increasing patients' safety through the development of an AI / ML- powered predictive tool that will be trained with multi-omics, genetic and non-molecular biomarkers.

1.1 Objectives and ambition

Relation to work program: Horizon-HLTH-2022-TOOL-11-01, Optimising effectiveness in patients of existingprescription drugs for major diseases with the use of biomarkers

Call description
Scope: The applicants should perform the clinical validation of qualified biomarkers (not limited to molecular biomarkers) that will enable the identification of appropriate patients to ensure an effective and efficient use of existing pharmaceuticals in the treatment of major diseases and conditions. The relevant biomarkers should allow providing the right medicinal product, at the right dose and the right time, according to the concept of personalised medicine, taking into account, among others, differences of sex, age, ethnicity and gender identity. This topic refers to medicines that are already on the market and not to the validation of biomarkers for the development of new medicinal products. It addresses broadly prescribed medicines for major diseases and conditions, including but not limited to cardiovascular diseases. A condition is that preliminary studies or publications have demonstrated that the pharmaceuticals considered are efficient in less than 50% of the population treated. The applicants should consider existing guidelines, standards and regulations, as appropriate. Synergies with relevant European Research Infrastructures are encouraged.
OPADE objectives are to: - Establish patient profiles to predict and optimise the efficacy of the treatments prescribed to patients with MDD with an increase in the remission rate and reduction of impairment of real-life functioning. - Unveil a correlation between neuroinflammatory indices, target indicators of the microbiome, metabolomic, immune-profile linked, epigenomic, enzymatic algorithms with symptomatic MDD pictures - Identify and evaluate biomarkers that may represent predictive indices of recurrence - Improve diagnostic accuracy for primary prevention (early biomarkers). -Evaluate retrospectively - through accurate anamnesis, the onset of depressive symptoms in adolescence. - Determine to what extent do blood biomarkers correlate with other specific biomarkers (metabolomic, proteomic, genomic) **OPADE Approach:** The efficacy of the antidepressant prescribed to patients with MDD is reported to be around 40%, letting 60% of the patients in a long medical vagrancy. We will run prospective observational clinical studies (paediatric and adults) to determine panels of molecular and non-molecular biomarkers that help predict antidepressant efficacy from the first week of treatment prescribed. We will recruit MDD patients in 4 different groups (14-17 years; 18-30 years; 31-39 years; 40-50 years) to make sure that our study consider the pathology in teenagers (50% of the cases globally). MDD affects more women than men. We will respect the sex balance in each group of our study. We will enrol patients with an established diagnosis of MDD. We will assess the cognitive status of the patients and collect biological fluids (blood, stool) to establish the p's multi-omic and immune-mediated profiles. Patients are followed-up for 24 months. Using AI-powered analysis correlating multi-omic analysis (MGB axis: microbiome, metabolome, proteome, epigenome, transcriptome, enzymatic profile), socio-demographic and clinical outcomes, OPADE partners will develop a AI-predictive tool (companion diagnostic-like) that will further help the physician in the decision-making process to identify the right treatment for a specific patient profile at the right dose, providing personalised treatment to each patient.
Expected OPADE outcome
Scope: Diagnostics industries move towards market approval for companion diagnostics
1/ Deploy an AI-powered predictive tool (companion diagnostic-like[13]) in clinical practice for the prescription of anti-depressants. OPADE AI-powered predictive tool will be a class C medical device under the In vitro diagnostic classification. 2/ Validate a patient tracking tool for mood assessment using brain biomarker. 3/ Validate a patient engagement digital tool that can be deployed in any patient community to enhance clinical study outcomes.

[13] *Per regulatory definition a companion diagnostic is a digital tool developed in parallel with a new drug. As the call specifies that we have to target existing drugs, we decided to call our digital tool 'AI-powered predictive tool'.*

Scope: Regulatory authorities approve companion diagnostics and make recommendations for the prescription of existing drugs. Health care providers use biomarkers with existing pharmaceuticals to treat more efficiently and cost-effectively patients, with less adverse effects
OPADE long term outcomes: 1/ Validate our AI-powered predicting tool to be deployed in clinical practice to enhance clinical efficacy of the selected anti-depressant 2/ Validate our algorithm with all the other anti-depressants available on the market 3/ Propose new set of biomarkers that can guide the development of new antidepressants

OPADE consortium has defined the following KPI (Table 1) that will help to track project advancement.

Table 1. OPADE KPIs

	Lead	M6	M12	M18	M24	M30	M36	M42	M48	M52
Clinical centres activated	EBRIS	1	6							
Nb of patients enrolled	UNISA	10	150	250	350					
Nb of patient visits	UNISA	20	450							
Nb of patient empowerment sessions	MMH	1	40	100	150	200	300	400	500	
Nb of EEG distributed	CEP	10	150	250	350					
Ng of samples collected	All	60	400	1500	2100	2700	3750	4500	5250	
Set of questionnaires filled	UNISA	15	350	600	1000	1500	1750	2000	2100	
Set of biomarkers	EBRIS	15	250	350	400	500	700	1000	1300	1400
Clinical report	EBRIS					Interim				1
Publications open-access	All				2		4			7
International presentation	All		1	3	5	7	9	12	17	23
Stakeholder events	BIOK				1		2			3

Positioning of the project

The major technology results of the project are outlined below, in relation to their Technology Readiness Levels (TRL) at project start and project combination.

Type	Output	Leader	TRL start	TRL end
Analysis results	Multi-omics analyses reveal associations between patients' microbiome, immune-profile linked epigenome, metabolome, enzyme profiles and efficacy of selected anti-depressants in MDD in teenagers and young adults	AIE	6	8
Biomarker	Gut microbiome biomarkers for patient stratification and treatment efficacy	PBIO	7	9
Biomarker	Immuno-profile for patient stratification and treatment efficacy	PRO	6	8
Software	AI-powered predictive tool to guide psychiatrists /GPs in their choice of anti-depressants to treat MDD	AIE	5	7
Software	Patient empowerment tool ready to be deployed in any type of clinical trials	MMH	6	9
Hardware	Headset to measure EEG	CEP	6	8
Software	AI to assess emotion based on EEG	CEP	6	8

1.2 Methodology

Primary care is the major access point for depression treatment, causing alarming numbers on depression. Research study demonstrate that by boosting to 80% (around 10% today) the treatment adequacy, the remission rate will double, reaching 12%. OPADE will develop a AI-powered predictive tool that will be deployed to support decision-making for the healthcare providers to decide on the best treatment option for a specific patients (targeted therapy).

OPADE will focus on the gut brain axis that is recognised as a major player in mood disorders.

Overall methodology

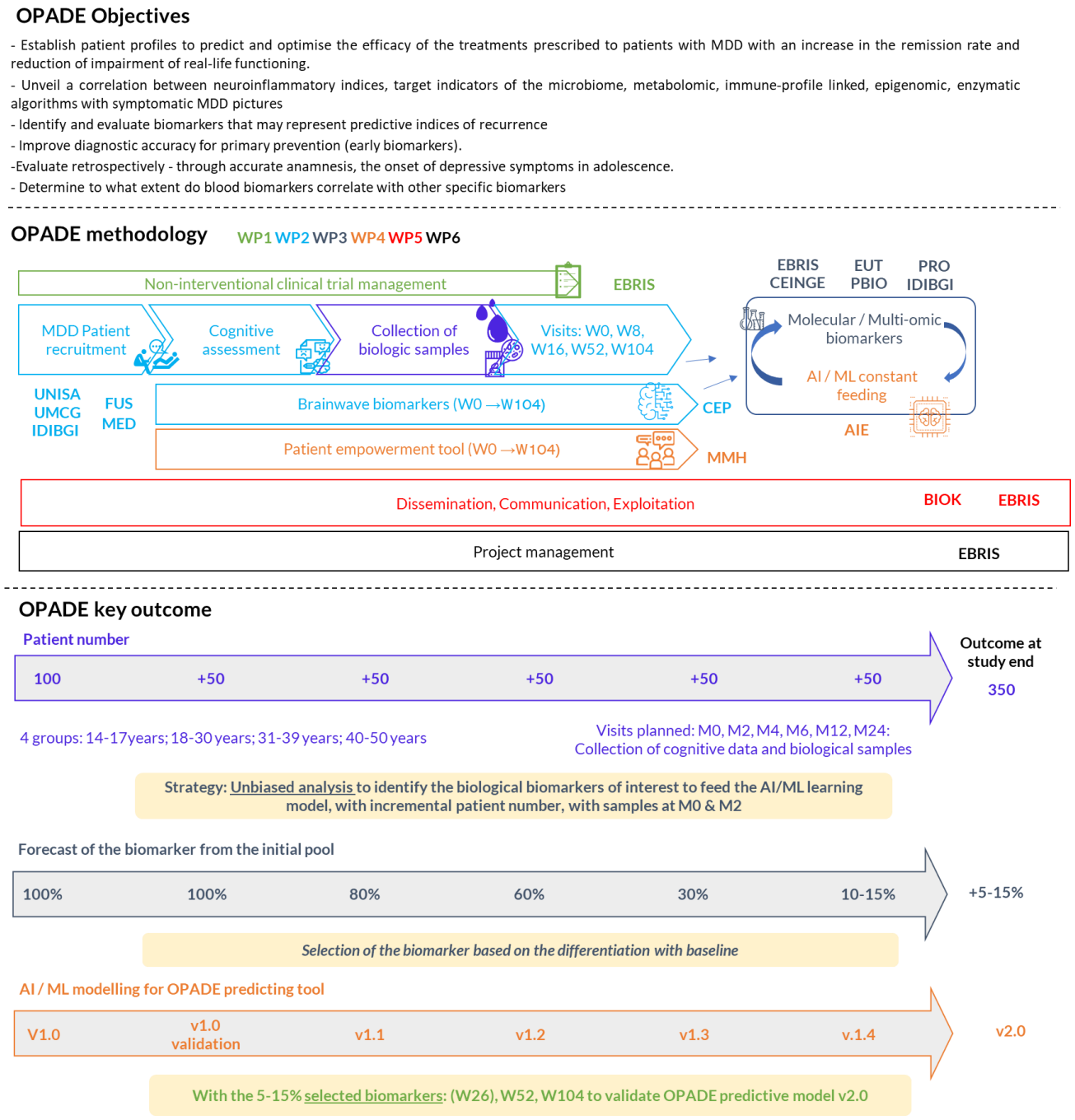


Figure 4. Global methodology of the OPADE project

Clinical trial design

OPADE's clinical strategy is to lead observational prospective clinical trials on paediatric and adult populations. We will recruit 350 patients diagnosed with MDD is 10 clinical centres from 5 different countries (UNISA is an internal consortium of 6 Italian centres, FUS - Columbia, ACC – The Netherlands, IDIBGI - Spain, MED - Turkey). The 350 patients are divided into 4 groups:

- 14-17 years (paediatric trial): 70 patients
- 18-30 years (adult trial): 100 patients
- 31-39 years (adult trial): 90 patients
- 40-50 years (adult trial): 90 patients

6 visits are planned: M0 (enrolment), M2, M4, M6, M12, M24. At each visit, the patient fills in the different questionnaires (Table 2) with the support of the physician / nurse. Biological samples (blood, stool, urine) are collected and stored to be further shipped to the OPADE analytic partners.

The primary aim of the clinical trial is to establish patient profiles to optimise antidepressant efficacy, by correlating neuroinflammatory indices, target indicators of the microbiome, metabolomic, immune-profile linked, epigenomic, enzymatic algorithms with symptomatic MDD pictures.
The secondary aim is to identify biomarkers that allow to spot recurrency for a specific patient.

Remission assessment

Within the 4 patient groups, OPADE will compare the remission and non-remission of symptoms at each timepoint: M2, M4, M6, M12, M24. The commonly used criteria for remission in clinical trials are based on threshold, or cut-off, scores from standardized scales. Full remission is defined as a relatively brief period during which the individual is asymptomatic. Asymptomatic is not defined as a complete absence of symptoms but instead is defined as no more than minimal symptoms. According to the literature, remission is defined as a score of ≤7 on the 17-item Hamilton Depression Rating Scale (HAM-D). Among the non-remitted group, the proportion receiving antidepressant augmentation with another antidepressant medication of a different class or other medication was also assessed.

Socio-demographic and clinical anamnestic assessment

For all subjects, the socio-demographic information will be collected by using a form developed ad hoc: age; gender; ethnic group; education; employment status (employed, not seeking employment, unemployed, missing); housing status (homeowner, tenant, other); financial strain (doing okay financially, just about getting by, struggling financially, missing); highest level of educational attainment (bachelor's degree or above, A-level of diplomas, GCSE 1016, none or other, missing); marital status (married/cohabiting, single, no longer married); social support; age of disease onset, illness course, pharmacologic treatments, food patterns. All available sources of information (patient, family, medical records and mental health workers) will be used to complete the form.

Assessment of psychopathological aspects

The Hamilton Rating Scale for Depression (HAM-D), is a multiple-item questionnaire used to provide an indication of depression, and as a guide to evaluate recovery). The questionnaire is designed for adults and is used 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 and adults, based on a two-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.
We will ass electrocardiogramme, history of cardiovascular diseases (including year of diagnosis), body mass index (BMI) and lifestyle (Exercise, diet, smoking).

Assessment of the person's resources

Assessment of stigma associated with mental illness: the Internalized Stigma of Mental Illness (ISMI), which assesses the internalized experience of stigma and self-evaluation.
Relationship with mental health services: the Service Engagement Scale (SES), which includes 16 items grouped into 4 subscales: a) availability; b) collaboration; c) help-seeking; d) adherence to treatment.

Assessment of functioning in real life and Quality of Life

Global Assessment of Functioning (GAF) scores the severity of illness. GAF is known worldwide and it is Axis V of the internationally accepted Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (DSM-IV-TR). 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 was measured with the Childhood Global Assessment Scale (CGAS). Furthermore, social and role functioning was specifically assessed with the Global Functioning: Social

Scale (GF: Social) and the Global Functioning: Role Scale (GF: Role) to obtain differential measures of functioning. The GF: Social and Role scales, which provide clinician-rated single overall scores, represent parallel (one targeting social, the other role) well-anchored scales that take age and phase of illness into account, enabling 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-appropriate intimate relationships and involvement with family members. GF: Role rates level of performance in primary role: school, work or homemaker. 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 eight multi-item variables: physical functioning (ten items),social functioning(two items), role limitations due to physical problems (four items), role limitations due to emotional problems(three items), mental health (five items), energy and vitality (four items),pain(two items),and general perception of health (five items). There is a further unscaled single item onchanges respondents' health over the past year. 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.

Digital tool for patient empowerment: Turn stories into data

MMH, OPADE partner, is using mathematical modelling to turn patient stories into data. Patient feedback is collected through the OPADE patient community (respecting GDPR). Patients share their story as they would do with a friend, will meet on a regular basis (frequency to do optimised based on patient recruitment rate) with their peers to support each other. Patients have access to their dashboard and can compare with patients following the same journey.
Stories are collected through a chatbot (accessible from any device) where patients indicate their journey: what happened, when, and how they felt. With natural language processing and medical ontologies (SNOMED-CT) key information (e.g. symptoms, clinical tests, feelings) are extracted from the free text written by patients in the chatbot. MMH's tool use process technology to mine the overall journey of the population from the single traces (journeys) of individuals. The result or the analysis is displayed in real time on a dashboard that is accessible to patients (in a simpler form, Figure 5) and in the full details to the OPADE research team.

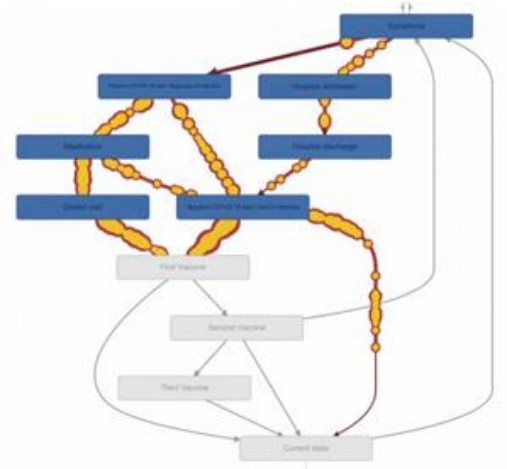


Figure 5. MMH mathematical modeling model that transforms patient stories into data

MMH tool will allow to spot inefficiencies across the clinical trials, understand MDD patient needs and monitor patients from all countries involved on OPADE clinical trial. MMH will provide patient questionnaires in own patient language.

Digital tool for patient engagement: Peer-to-peer support groups

MMH supports patients across the OPADE study with self-help groups among patients with a very similar story (Figure 6). During the entire duration of the study, patients will be invited to join a virtual lobby (with their video on or with their avatar) to support each other. The online sessions - moderated by professionals – will enable the participants of the study to discuss their health conditions with others who can understand what they are feeling.
There is evidence that internet-based peer-support groups for chronic patients can result in less reduction in anxious preoccupation, helplessness, confusion and depression.

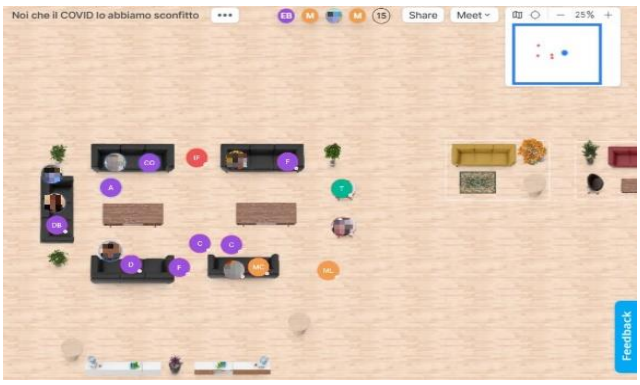


Figure 6. Visual of the chat room by MMH

Table 2. Summary of the scales used during OPADE clinical trials to assess the psychological status of the patients

Scale	Time to fill in
Hamilton Depression Rating Scale (**HAM-D):** Depressed mode, Feelings of guilt), Suicide, Insomnia early / middle / late, Work and, Retardation psychomotor, Agitation, Anxiety – psychological, Anxiety – somatic), Somatic symptoms gastrointestinal / general, Genital symptoms, hypochondriasis, loss of weight, insights, diurnal variation, depersonalisation and derealisation, paranoid symptoms, obsessional/compulsive symptoms.	17 items 5 min
Beck Depression Inventory-Second Edition **(BDI-II):** sadness, discouragement, failure feeling, satisfaction, guiltiness, self-punishment, self-disappointment, self-criticism, suicidal thoughts, crying episodes, irritation, interest in others, decision-ability, self-esteem, ability to work, sleeping status, tiredness, appetite, weight loss, health worrying, libido	21 items 5 min
Montgomery-Asberg Depression rating scale **(MADRS):** Apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, suicidal thoughts	10 items 3 min
Mood spectrum-self report-current (MOODS SR): current or previous (during childhood) 3-5 day period of feeling of frustration, loneliness, nostalgia, introverted attitude, hard to take rejection, episodes of crying, complaining, purposeless, loss of interest, depressed mood with/without medications, use of alcohol, marijuana, similar substances, anti-anxiety drugs, loss of interest in social life, in friendship, romantic, hobbies, sense of humour, sensibility to small things, suicidal thoughts, inappropriate behaviour with money.	161 items 15 min
Internalised Stigma of Mental illness **(ISMI):** belief on other people behaviour face to mental illness, feeling of inequality, discrimination, embarrassment, understanding, loneliness, people reaction, unfairness, global self-esteem	29 items 7 min
Service engagement scale **(SES):** persistence in work / hobbies, enthusIDIBGIm, self-proudness, energy, morning entrain, happiness, physical engagement, emotional engagement, cognitive engagement.	14 items 5 min
Global assessment functioning **(GAF):** functioning in daily activities, interest in social activities, symptoms, social impairment, behaviours, danger of hurting self or others, impairment in communication,	10 items 6 min
Childhood global assessment scale **(CGAS):** functioning level in all are (home, school, with peers), need for supervision,	4 items 5 min
Short form 36 adult form **(SF36):** physical and social functioning, physical and emotional role limitations, mental health, energy/vitality, general health perception, pain	36 items 7 min
Paediatric quality of life inventory **(PedsQL):** physical, emotional, social, school functioning, physical health, psychosocial health, self-report, eating activities, fatigue, movement and balance, pain and hurt, speech and communication	23 items 7 min
Treatment-resistant depression (TRD): symptom duration, severity, treatment failure, dose augmentation, use of electroconvulsive therapy	5 items <1 min
OPADE dedicated questionnaire: age, gender, ethnical group, education, employment status, housing status, financial strain, highest level of educational attainment, marital status, social support, age of disease onset, illness course, pharmacologic treatments, food patterns. All available sources of information (patient, family, medical records and mental health workers) will be used to complete the form	15-20 items 8 min
OPADE patients will fill in these different questionnaires at each visit (M0, M2, M4, M6, M12, M24) - total estimated time to fill them all: 1h20	

Digital tool for patient monitoring: Real-time emotion analysis

CEP, OPADE partner, provides real-time emotion analysis facilitating patient monitoring and the supervision of treatment effectiveness via brainwaves to provide an objective indicator, avoiding the possible memory bias and subjective-psychological bias. CEP's solution consists of an electroencephalographic (EEG) device, a mobile application for patients, and a platform for the medical professionals, powered by both cloud and edge computation. CEP's EEG device is in the forms of an eyewear adapter and ear hooks that are portable and discrete, facilitating continuous EEG measurement throughout the patient's daily life. Furthermore, CEP's EEG device equips with novel dry electrodes that assure EEG signals in medical-grade quality (over 92% correlation comparing the medical wet electrodes) in various types of activities. The EEG locations applied in CEP's EEG devices are based on the 10-10 international system and have been proven to be scientifically the most efficient and adequate EEG positions for emotion recognition. CEP's mobile application works as an information hub for patients, such as providing an overview of emotion analysis, the instructions for relaxation exercises, and most importantly documenting patient's emotional feedback. Patient's emotion feedback serves three purposes - patient's self-documentation as a part of psychotherapy, as a patient's self-labelling for his/her emotion pattern, and as feedback for OPADE clinical trial. The acquired EEG data is processed by artificial intelligence using convolutional neural networks (CNN), and translated into different mental states, i.e. emotions or more specifically valence and arousal levels. Knowing that EEG patterns vary across groups such as ages, the self-labelling of the patient's emotion assures a powerful and polyvalent emotion recognition. With the patient's self-labelling and the patient's basic information, CP's algorithm is able to conduct individual analysis focusing on different groups of patients such sex and gender, age, culture, etc. and derive their respective responses during OPADE clinical trial. This continuous and group-focused analysis is able to provide a full scope of treatment effectiveness throughout OPADE.

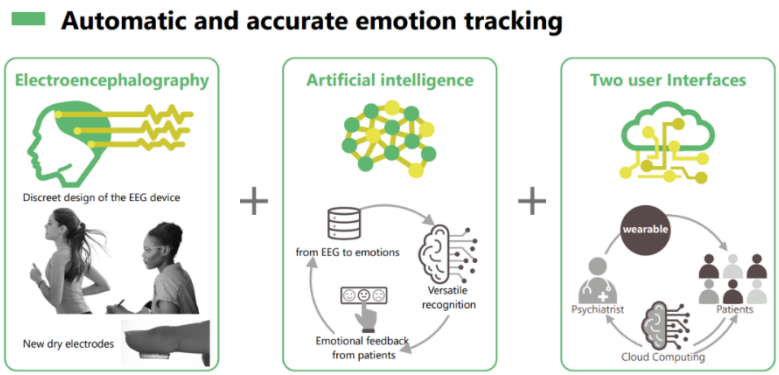


Figure 7. CEP device is deployed to track patient emotion in real time using a discreet wearable

On the other hand, CEP is able to identify the brainwave biomarkers corresponding to the given molecules of the said antidepressants and further correlate to the immune responses within OPADE's framework. Furthermore, in addition to the given parameters of antidepressants, CEP will also test the impact of the patient's self-engagement on the effectiveness of antidepressants - if the patient pays attention to his/her emotional evolution on the mobile application throughout the treatment or not.

Overall, CEP will examine the impacts on the variants of antidepressants and the accompanying factors (self-engagement, relaxation exercises involving cognitive behavioural therapy) on different groups of patients (gender, age, culture, pathology, etc).

AI-powered predictive tool

Psychiatry has evolved to a stage where complex patients data can be collected at a decreasing cost and can be used to solve major problems in the field. In the context of the depression and the relationship with the microbiome (Figure 8), the number of data generated can rapidly become unmanageable. To make the data speak, one needs advanced Data Science and AI knowledge, usually out of the area of expertise of the biomedical teams. Fortunately, there is a strong trend in AI and digital automation toward low- or no-code platforms to democratize their use. Following this trend, we will increase the level of automation in the project field. AIE partners together with all the biomedical partners (ERIS, PBIO, EUT, PRO, CEINGE) will formulate the project goals as Data Science problems, from the beginning. Using tools like 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. The AutoML/AI algorithms inside Python packages like TPOT, Pycaret, Autokeras, will be applied to the data to develop predictive models. Explainable AI (XAI) 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. The predictions will be expressed as "If-Then" conditional rules. 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. 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, 1-D Convolution Neural Networks, and also the algorithm developed by AIE (RODES – Reversing Ordinary Differential Equations Systems). This platform will dramatically boost the research in the field.

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. 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.

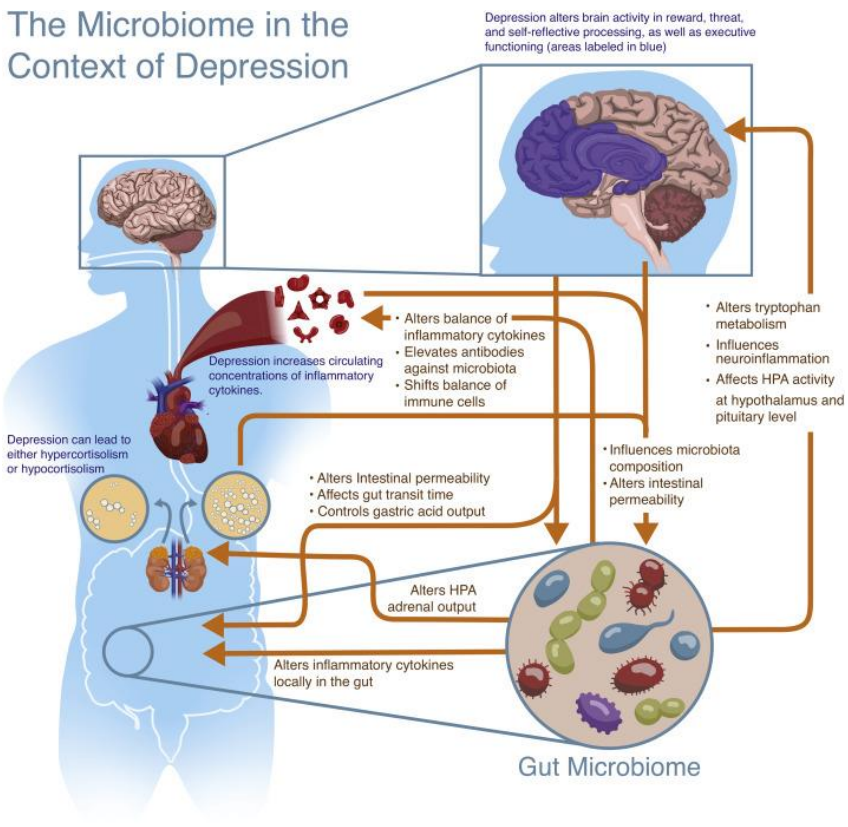


Figure 8. Microbiome and depression. Complex pathways

We will develop several iterations of the OPADE AI-predictive tool trained at 2 time points, M0 (baseline) and M16 (recognised time point for anti-depressant efficacy):

- v1.0 will be trained with 100 patients and 100% of the biomarkers selected for their interest as described in the proposal (unbiased analysis)
- v1.0 will be validated with 50 other patients and 100% of the biomarkers selected for their interest as described in the proposal (unbiased analysis)
- v1.1: we will train the model with 50 more patients (200 total) and intend to isolate 80% of the biomarker of interest
- v1.2: we will train the model with 50 more patients (250 total) and intend to isolate 60% of the biomarker of interest
- v1.3: we will train the model with 50 more patients (300 total) and intend to isolate 30% of the biomarker of interest
- v1.4: we will train the model with 50 more patients (350 total) and intend to isolate 10% of the biomarker of interest. With this last iteration, OPADE consortium will have established a patient profile of interest.
- For the 350 patients, the 10% of the identified biomarkers will be analysed on patient samples collected at the time point M12 and M24 and integrated / analysed with the AI-predictive tool.

- Based on the results obtained (potential interest), the number of biomarkers identified and the associated budget, the time points M3 will be analysed as well.

Data will be correlated with patient answers to the different questionnaires and EEG analysis to assess anti-depressant efficacy. Using this method, OPADE consortium is optimising the total project budget (partners have budgeted based on the forecast of the biomarker selected) and will stop to perform analysis that have no interest in determining anti-depressant efficacy.

Inflammatory biomarkers and growth factors

Commensal microbiota and the mammalian immune system have a multitude of interactions. The microbiome plays critical roles in the training and development of major components of the host's innate and adaptive immune system and the immune system orchestrates the maintenance of key features of host-microbe symbiosis. Microbiome-immunity cross-talk and their role in the MDD and the response to antidepressant is a key aspect. Using multiplexed immunoassays, EUT will analyse several inflammation-related biomarkers (cytokines, interleukines, see T3.1 for the detailed list) and several growth factor within patient plasma sample.

Metabolomic analysis

The circulating metabolome has been reported to be a key source of biomarkers of depression and the gut microbiota/metabolome has been suggested as a critical influencing factor. To investigate the reasons that underlie the asynchronous development of MDD, we will correlate the concentration of tryptophan, serotonin, 5-HIAA, kynurenine, kynurenic acid, L-acylcarnitines and phenolic compounds. EUT will use liquid chromatography coupled to triple quadrupole mass spectroscopy.

Lipoprotein analysis

Lipoproteins influence the content of the microbiome and the dysbiosis. EUT will use the ^{1}H-NMR platform to establish the lipoprotein in patient plasma samples.

Metagenomic Abundance Profiling

PBIO will determine the microbiome composition of the MDD patients. To this end we will use the dynamic Metagenomic Abundance Profiling (MAP), as developed and commercialized by PBIO. MAP accurately identifies and quantifies all species in a microbial community in a single analysis, including critical fungal and viral components, rather than just bacteria. With greater speed, lower cost, and much better accuracy of identification, we can solve the challenges now facing the field: a super-abundance of samples and clinical needs, and a metagenomic sequencing technology that cannot keep up in terms of speed, price, or accuracy. PBIO will carry out a full microbiome population analysis, generating a catalogue of species and up to specific strains, with absolute and relative concentrations of each species. **Measuring this full profile throughout the trial will allow tracking of the human microbiome on the timescale of its dynamics, monitoring the therapeutic intervention on a personal level**. Analyzing patient samples at different time points will provide a detailed insight into how the microbiome reacts to the anti-depressant, and how this correlates with patient profile.

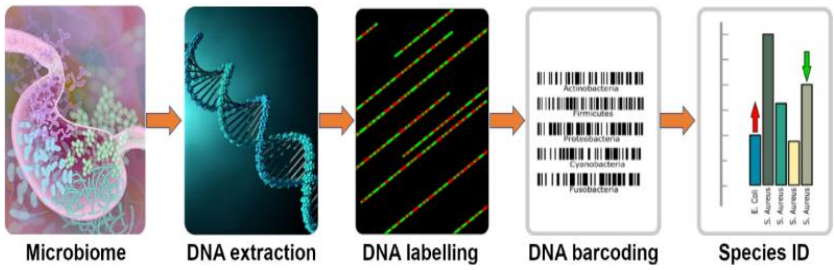


Figure 9. MAP analysis by PBIO

Transcriptomic analysis

Circulant RNA have been shown as imbalanced in MDD patient plasma samples. Using spectrophotometry methods, EBRIS & CEINGE will quantify the miRNAs.

Epigenomic analysis

We will perform methylome analyses on genomic DNA extracted by blood and saliva. Methodologic approach will consist in the methylation state of 850.000 CpG sites per sample and bioinformatic analysis. 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. 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.

Pharmacogenetic and long QT phenotype

Genetic analysis will be conducted by IDIBGI through a saliva sample. Cardiovascular risk factors will be obtained through a blood sample, electrocardiogramme and data extracted from clinical records.

Hormonal / cortisol analysis

Cortisol is analysis on saliva sample through radio-immuno assay.

Immunoprofiling by MVA

MDD is characterized by heterogenous clinical phenotypes and it is unknown whether there are immunologically measurable indicators of these heterogenic conditions. However, given the size of the available clinical cohorts and the high-quality clinical data associated with diagnosis and prognosis suggest it is highly likely that new clinically useful toolsets can be generated. It has recently been shown that MVA, a next-generation random peptide phage display assay, provided highly antigenic antibody response profiles from peripheral blood (immune profiles) for debilitating, neurological diseases. The strong preliminary data on different neurological conditions with autoimmune and environment-triggered effects suggest high chances of successful generation of the high-throughput diagnostic immune profiles associated with MDD. Protobios will perform immune epitope profiling by MVA technique in samples (n=700 untreated and matched treatment cohorts) obtained from partners. MVA biomarker leads will be assessed for accuracy using independent experimental and *in silico* methods.

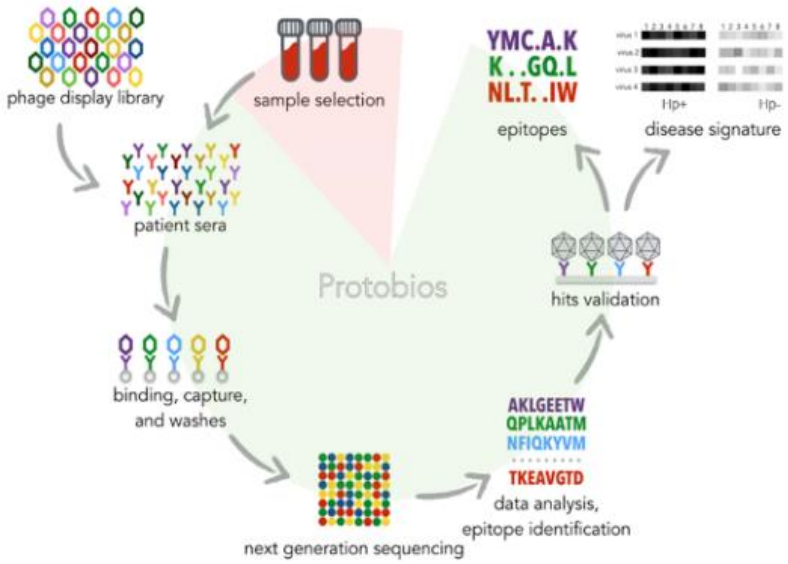


Figure 10. MVA analysis by PRO

National or international R&I activities linked to the project

We have identified the most relevant patents, publications and databases that serve as basis in the definition of OPADE basic principles and objectives.

Project	Partner
GEMMA: Gut-brain-axis to study autism	EBRIS
IntelMark 2.0: Develop AIE technology agnostic molecular diagnostic platform	AIE
Perseus MAP: EIC Accelerator blended finance to develop MAP central lab	PBIO
Key publications	
A Delphi-method-based consensus guideline for definition of treatment-resistant depression for clinical trials, Sforzini (…) Fagiolini.	UNISA
The smallest sample size for the desired accuracy, Floares et al., 2017	AIE
Using computational intelligence to develop intelligence clinical decision support systems, Floares et al., 2009	AIE
Optimizing prediction of response to antidepressant medications using machine learning and integrated genetic, clinical, and demographic data, Taliaz et al. 2021	-
Unravelling the antimicrobial action of antidepressants on gut commensal microbiomes, Chait et al., 2020	-
Databases	
https://www.gale.com/intl/databases-explored/social-issues/depression	Open
OmicsDI	Open

Inter-disciplinary approach

Addressing a complex subject, OPADE tackles several human-centric scientific, societal, technical and

technological subjects. A multi-disciplinary expert consortium has been constructed with competences in all necessary disciplines: 14 partners gathering omics, clinical, patient management, whose complementary knowledge in drug development, diagnostics -omics, clinical, technical, social and regulatory experience will allow addressing the challenges of the project.

Integration of Social Sciences and Humanities

Social Science and Humanities (SSH) are a core dimension in the design and implementation of research projects related to Health providing economic, social and psychological analysis for developing new models. Using SSH methods fosters the social acceptance by the people involved in the clinical studies, in terms of the design and evaluation of the explainability, acceptance, usability of the diagnostic systems and the pharmacological efficacy evaluation, thereby increasing the chance of successful trials (WPs). OPADE plans to analyse the patient's perceptions through interviews in the trial design and the evaluation of their satisfaction from their experience and outcomes, including perception of value. Social Sciences methods (Health Economics, Business and Project Management, Sociology) will also be used in the evaluation of the proposed outcomes (treatment, omic models, diagnostic device, digital tool) from the perspective of its impact on the healthcare systems. OPADE includes partners with expertise in SSH, including Social Innovation, Patient engagement (MMH, CEP) and Communication and Dissemination (BIOK), integration of Gender in Research (EBRIS) and Health Economy (EBRIS), covering the full spectrum of targeted challenges.

Sex and gender analysis

Women report more depression disorders than woman with a prevalence of 1.64:1. Depressed women were more likely to report "increased appetite" (15.5% vs. 10.7%), being "often in tears" (82.6% vs. 44.0%), "loss of interest" (86.9% vs. 81.1%), and "thoughts of death" (70.3% vs. 63.4%), while men have tendency to external behaviours such as aggressiveness, addiction, and risky behaviour. Numbers unveil that men diagnosed with MDD commit suicide more often than women. Epidemiology and other abnormalities are summarised in Figure 11.

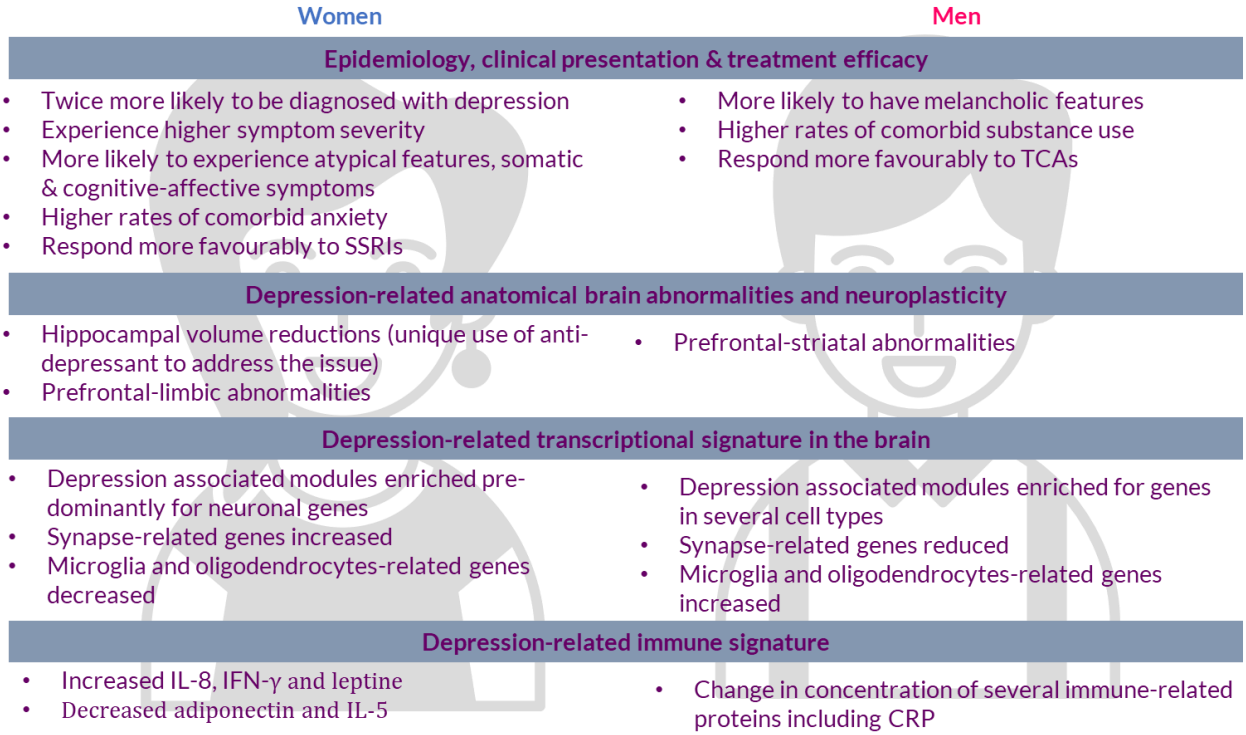


Figure 11. Depression characteristics in women (left) and men (right)

Open science practices

Open science will be the main driver criteria of communication and dissemination activities under the OPADE project. BIOK, dissemination leader, will establish the dissemination strategy since project start (dissemination plan available by M3). It will include **early and open sharing** of research (through preregistration, registered reports, pre-prints, or crowd-sourcing) **research output management** including research data management (as described in the Open science section) and measures to ensure **reproducibility** of research outputs. As labs data are used to generated OPADE AI/ML prediction tool,

data will be published after clearance by the consortium that IP will not be endangered. EBRIS, exploitation leader will ensure the IP protection.
We will provide open access to research output and we will publish peer-reviewed publication in open access. We will make available our research articles at the latest within 30 days after there were generated, through open-access channels. We will provide on-line access to scientific and clinical information, with publication in peer-reviewed scientific journals. The consortium will use PsychData, OpenAir, GitHub, as repositories for peer-reviewed articles published by the consortium to ensure the largest possible impact among researchers, policy-makers and businesses. The consortium will also leverage specific Open Access event repositories. OPADE partners will publish project results on an open access database.
Each partner will ensure open access to the deposited publication (via the repository), if an electronic version is available for free via the publisher, or within 6 months of publication. The partners will also ensure access to the bibliographic metadata that identify the deposited publication (including terms under the grant agreement, the name of the action, acronym and grant number; the publication date, and length of embargo period if applicable, and a persistent identifier). However, the partners will retain their copyright and grant adequate licences to publishers, based on creative commons licenses.

Data management and management of other research outputs

Data management activities are part of WP6 - Management and will start with the formal release of a Data Management Plan (D6.2) at M3. The project will follow the open data management guidelines of the Horizon Europe Programme and specifically:

- The project will deposit the research data in a research data repository that facilitates linking publications and underlying data through persistent identifiers and data citations.
- The project will take to enable third parties to access, mine, exploit, reproduce and disseminate (free of charge for any user) this research data by attaching Creative Commons Licences to the data deposited
- The project will provide information via the research repository about the tools available to the users that are needed to validate the results, *e.g.* specialised software or software code, algorithms and analysis protocols, and wherever possible, will provide these instruments.

Data management preliminary approach (full DMP to be provided at M3)
Type: Clinical anamnesis are collected. Patient stories are collected to be transformed into data. EEG data are collected to assess mood disorders. Patient samples (blood, stool…) are collected during the project to generate patient' omic, genetic and immune profiles. Analysis results on patient samples are generated. Non biological and biological biomarkers are used thought the AI / ML tool to generate predictive tools.
Findability: Patient data are anonymized since collection to prevent the identification of an individual by a non-accredited personal. Only the referent physician has access to patient name. A common code (ex: patient -01) will be used to label all the analysis over the different centres.
Accessibility: We will publish research results / outcomes in open-access journals. Anonymised raw data will be made available on public database if it does not infringe IPR generated by the consortium partners.
Interoperability: Within the consortium, genetic, omic, immuno data are exported in open, document tabular format accessible to humans and standard software and AI / ML tool.
Reusability: Lab' partners will aliquot samples that will be available for analysis. Clinical partners will respect GCP and appropriate ontology to extend analysis beyond project scope.
Curation and storage: EBRIS is responsible for sample storage. MMH is responsible for processing and storage of patient's stories. CEP is responsible for EEG patient data collected and generated results. EUT, EBRIS, PRO, PBIO, CEINGE, IDIBGI are responsible for the generated lab data. AIE in responsible for the data generated through OPADE AI-powered predictive tool.

OPADE project will handle high-risk data though AI, in particular patient data analysis. AIE and CEP, OPADE partners will ensure the throughout the development process:

- Model reliability (AI technical robustness): we will address the ability of models to avoid failure or malfunction, either due to edge cases or malicious intentions. Key vulnerabilities will be identified, and technical solutions implemented, to ensure that autonomous systems do not fail or be

manipulated by an adversary. To do so, we will use libraries dedicated to adversarial ML, allowing rapid crafting and analysis of the attack, defence, and detection methods for ML models.

- Model fairness (AI social robustness): diversity in training data has a major influence on whether a neural network is able to overcome bias, but at the same time dataset diversity can degrade the network's performance. We will identify and tackle the biases that are introduced in the data, ensuring that a model's predictions are fair and do not unethically discriminate. To do so we will use open-source libraries to help detect and remove bias in machine learning models (there are comprehensive set of metrics for data sets and models to test for biases, explanations for these metrics, and algorithms to mitigate bias in data sets and models)
- Model explainability (AI transparency): we will document the AI processing chain, including technical principles and descriptions of the data used for model design. This also includes elements related to understanding and interpretability and explainability of the models. We will strive to give an improved understanding of the model by clarifying how the model works to 1) data scientists for detecting, avoiding, and removing its failure modes, 2) to SMEs and customers for earning public trust in the algorithm and 3) to policy-makers for introducing effective policies to regulate the technology. To do so we will use available toolkits including three classes of algorithms (local post-hoc, global post-hoc, and directly interpretable explainers) for models that use image, text, and structured or tabular data.
- Data protection (privacy-preserving AI): we will preserve the security of data used in artificial intelligence models. In the case of sensitive data, e.g., personal data, risks will be managed by applying appropriate organizational and technical controls. Data is a key aspect in artificial intelligence techniques, and the widespread use of data management systems, which has been enabled by the digitization of services, has led to the emergence of useful principles for properly storing and managing this data. We will follow the data governance concepts outlined in the GDPR Recitals 71, Article 4 and Articles 13 and 14, and 22.

Regulatory pathway

As a pre-requisite for commercial exploitation and use in clinical settings, our AI-powered predictive tool will be regulated according to the In vitro diagnostic regulation (IVDR – regulation (EU) 2017/746). The digital tool will be CE marked as a class C medical device. Under the leadership of AIE, the consortium will provide the documentation to ensure the certification by the notify body.

2. Impact

2.1 Project's pathways towards impact in HORIZON-HLTH-2022-TOOL-11-01

Expected outcome	OPADE results
Diagnostics industries move towards market approval for companion diagnostics.	1 AI-powered companion diagnostic ready to be deployed to support new drug discovery research with MGB emphasise 1 patient empowerment tool that can be deployed during clinical studies to collect patient feedback in their own language 1 medical device that drug efficacy in real time though EEG and ML, measuring patient mood
Regulatory authorities approve companion diagnostics and make recommendations for the prescription of existing drugs.	1 AI-powered predictive tool [14] that can be deployed for HCPs to identify the right treatment and the right dose for MDD patients based on their genetic, omic and immune profiles.
HCPs use biomarkers with existing pharmaceuticals to treat more efficiently and cost-effectively patients, with less adverse effects.	Multi-omic patient patterns are available based on blood / stool / urine analysis to determine the most efficient anti-depressant. Evolution of patient pattern is understood in regards of the treatment efficacy.

OPADE project will contribute to Key Strategic Orientations: Cluster one (Health) aims to contribute to towards two Key Strategic Orientations (KSOs) for R&I set by Horizon Europe's strategic plan 2021-2024, creating a more resilient, inclusive and democratic EU society (KSO-D) and promoting an open strategic autonomy by leading the development of key digital, enabling and emerging technologies, sectors and value chains (KSO-A).

[14] *Per regulatory definition a companion diagnostic is a digital tool developed in parallel with a new drug. As the call specifies that we have to target existing drugs, we decided to call our digital tool 'AI-powered predictive tool'.*

OPADE will contribute to KSO-D and KSO-A since project end, in 2023. Regarding the specific impact areas, OPADE will contribute, in the long term, to enhanced impacts on:

OPADE answers to strategic aspects of Destination Health
Europe's scientific and technological expertise and know-how, its capabilities for innovation in new tools, technologies and digital solutions, and its ability to take-up, scale-up and integrate innovation in health care is world-class.
OPADE will allow the clinical validation of several different digital tools analysis non-biological and biological biomarkers to enhance the positioning of EU non only on MDD segment but on the psychiatry field and beyond. Not less than 5 private entities (including 4 SMEs) are being part of this consortium with the goal to commercially exploit the assets generated during the OPADE observational clinical trial. Each company has a dedicated business plan and will also contribute to the exploitation of the collaborative exploitable assets generated during the study, the AI-powered predictive tool.
Citizens benefit from targeted and faster research resulting in safer, more efficient, cost-effective and affordable tools, technologies and digital solutions for improved (personalised) disease prevention, diagnosis, treatment and monitoring for better patient outcome and well-being, in particular through increasingly shared health resources
Through their referent physician, MDD patients will have access to their profile to determine the most appropriate anti-depressant. MDD patients will have access to a tool that can follow-up their mood fluctuations and brainwaves for a real-time monitoring of treatment efficacy. Patients enrolled in clinical trial will have access to empowerment tool to discuss their condition with patients receiving similar treatments and in similar health conditions.
The burden of diseases in the EU and worldwide is reduced through the development and integration of innovative diagnostic and therapeutic approaches, personalised medicine approaches, digital and other people-centred solutions for health care
25% of the EU population each year suffer from depression or anxiety; neuropsychiatric disorders account for 26% of the burden disease in the EU countries and for 40% of years lived with disability, with MDD as the main cause[15]. 50% of the chronic sick leaves. The EU costs are estimated to reach €170bn per year, with 50% of the MDD that remain untreated. Reputation of the anti-depressant needs t be cleaned with patients thinking such drugs can cause more harm than good. Through the use of personalised medicine, OPADE aims at correlating the omic, genetic and immune profiles of the patients to the right drugs that will be immediately efficient for each patient.
Both the productivity of health research and innovation, and the quality and outcome of health care is improved thanks to the use of health data and innovative analytical tools, such as artificial intelligence (AI) supported decision-making, in a secure and ethical manner, respecting individual integrity and underpinned with public acceptance and trust
All the data generated during OPADE aims at being correlated through AI / ML tool to issue an exploitable AI-powered predictive tool for personalised medicine. This predictive tool will be further regulated through the in vitro diagnostic regulation as a class C medical device.

The main target group of OPADE are the following:

Audience	Specific needs	Expected results
Patient & Patient' family	Need efficient treatment from day 1 of the diagnosis to improve / restore quality of life and decrease suicide rates	Identify the anti-depressant with the highest chance of success as early as possible based on patient' pattern
Healthcare providers (HCPs)	No insight to determine the optimal anti-depressant for a patient putting HCPs in the 'prescribe and see' situation	Available tool and biomarker sets to determine the anti-depressant with the highest chance of success.
Healthcare system	Need efficient treatment that will decrease the costs related to MDD and allow people to return into the workforce	Optimal costs of the needed analysis to establish patient patters to determine as early as possible the right anti-depressant.

[15] Depression in Europe: Facts and figure *(WHO)*

Researchers & Pharma companies	Understand gut-brain-axis mechanisms to unveil new targets and discover new efficient treatments.	Validated biomarkers to determine the efficacy of new molecules. Companion diagnostic & patient engagement tool to empower clinical activities.
General public	Anti-depressants have a bad reputation with severe side effects and a lack of efficacy.	A better understanding of the gut-brain-axis and the importance of the microbiome in the modern medicine
Standardisation bodies (ie CEN-CENELEC)	Dedicated / concrete standards for using digital technologies like AI / ML in health applications	Identify the limits and promises of the technology and improve the standards by sharing the results of the project

Impacts & expected outcomes

Year 1 corresponds to year 1 of the project, year 5 to year 5 and final of the project and year 5 corresponds to 2 years after project end.

Scientific impact: Creating high quality knowledge

- Feed the knowledge on the gut-brain-axis and the biomarkers of interest in mental health, starting with MDD.
- Correlate neuroinflammatory indices, target indicators of the microbiome, metabolomic, immune-profile linked, epigenomic, enzymatic algorithms with symptomatic MDD pictures
- Correlate biomarker kinetic with anti-depressant efficacy

Year 1: 2 publications in writing. 2 external KOLs appointed within OPADE advisory board.
Year 3: 2 publications accepted, 4 in writing. 6 presentations at international congresses. Key biomarkers of interest selected. Biomarkers without interest are also widely published to optimise research for other groups.
Year 5: 5 publications accepted, 6 in writing. 10 presentations at international congresses.

Scientific impact: Strengthening human capital on R&I

OPADE project will enrol 16-18 clinicians and 40 (10 PhDs, 10 post-docs, 20 permanent staff) researchers from 12 different countries.
Early-stage European researchers will be trained to multi-omics, immune profile and genetic analysis developing high-researched profile of interest for the pharmaceutical research and industry. The consortium will appoint each year an early researcher as a chair of the OPADE project Early Career Scientists group.

Year 1: 5 early researchers enrolled, 1 appointed young researcher part of the OPADE advisory board.
Year 3: 15-20 early researchers enrolled, 3 appointed young researcher part of the OPADE advisory board. Insightful research results used by OPADE researchers giving lectures to students. OPADE private partners explaining their entrepreneurship journey.
Year 5: 20 trained researchers ready to enter workforce. Long term collaboration established between OPADE partners that will be developed within future projects.

Scientific impact: fostering diffusion of knowledge and open science

We will collect existing data from major database and process them through our ML algorithm. Clinical and non-clinical outcomes will be published in open access journals.

Year 3: Video of the project is available on OPADE website to explain the project and the outcome. Patient associations are used as communication vectors to present results and the impact of the gut-brain-axis outside of the consortium.
Year 5: All publications are published on open-access journals, embracing the EU open-access policies. Ground breaking research results presented to students by OPADE teachers and external ones.

Societal impact: Addressing EU policy priority & global challenge

Contribution to 'Coalition for mental health and well-being': this EU initiative monitors the activities from the EC since 2012 , advocating for a comprehensive European mental health strategy and ensure the recognition of mental disorders at the political level. If the OPADE project is granted, we will reach out to them to collaborate with broad range of initiatives.
Mental health was included in the UN SDGs in 2015 as a global priority for the next 15 years. #FundaMentalSDG is 'committed to the belief that there can be no health without mental health'. Mental health is included in the SDG declaration and in the UNSDG3 in 3 targets: reduce by one third premature mortality from non-communicable diseases, strengthen prevention and treatment, achieve

universal coverage. 2 indicators are defined: decrease suicide mortality rate and the harmful use of alcohol. OPADE as a collaborative action directly contributes to the following UN SDGs:
3 – Good health & well-being: OPADE will optimise the efficacy of anti-depressant, allowing for patients to recover shortly after a depressive episode and to turn back to the work force and daily life.
1 – No poverty, 2 - Quality education, *8 – decent work and economic growth*: Poverty increases the risk of mental health and can be both a casual factor and a consequence of mental ill health. With OPADE, patients will benefit from the first attempt of the most efficient anti-depressant available based on his profile. Using real time assessment of the anti-depressant efficacy and detection biomarkers, recurrence of MDD will be rapidly identified to adapt treatment. As a direct consequence, the risk of patient mental disruption is limited, keeping her /him in the workforce and prevent vicious circle of poverty and impact on mental health.
5 – gender equality: Mental health concerns more women than men. Using a personalised approach based on patient profile, OPADE intends to propose the best treatment for women and men.
4 – Industry, innovation & infrastructure: A minimum of 5 exploitable assets will be deployed at the international level, using OPADE clinical results.

Year 1: 1 EU patient association appointed within OPADE advisory board.
Year 3: Communication campaign though OPADE social media channel to present the gut-brain-axis and the links with MDD.
Year 5: OPADE AI-powered predictive tool prevents the mis and over-use of medication, especially when there is no or low chance of success by proposing an alternative treatment for a specific patient. Personalised medicine considers the patient as an entire organism including the microbiota.

Societal impact: Delivering benefits & impacts
Develop a healthy European health union
MDD decreases by 10 years the life expectancy of the patients. 30% of the patients who get COVID-19 during pandemic report mood disorders as sequelae.
Decrease healthcare costs: In 2007, the economic cost burden of the depression alone amounted to €136.3bn in the European Economic area, including reduced productivity (€99.3bn) and €37bn in direct costs on the healthcare system. Every year, costs due to loss of productivity, decrease in employment rate costs €8b in France. By increasing remission to 24%, we estimate that OPADE AI-predictive tool will support the saving of €28bn yearly in indirect costs. Direct costs will be stable, and may even slightly increase with more people treated, based on their omic-profil. Total direct costs for depression ranged between $124 and 18,174 in the adults subgroup, between $358 and 14 225 in the elderly subgroup, between $2868 and 2883 in the adolescents subgroup and between $239 and 20,768 in the comorbidity subgroup.

Year 5: by improving treatment adequacy we can improve remission from 6 to 12%
Year 7: By improving depression recognition, treatment initiation and treatment adequacy, we can increase the success rate to 24%. Final webinar accessible to patients, patient associations organised to explain the OPADE study outcomes and impacts.

Societal impact: Strengthening the impact in society
Unaddressed mental health problems have a negative influence on homelessness, poverty, employment, safety and the local economy. Mental illness impacts productivity of local businesses, all leading to high healthcare costs. People suffering from MDD report twice as many work days of incapacity than people without depression. In 2014, employees suffering from MDD had an average 51.8 days lost due to depressive episodes. MDD that often starts in the childhood impedes the ability of children and the youth to succeed in school and lead to family and community disruption. OPADE aims at identify the best treatment options for teenagers and young adults, while most of the clinical guidelines on mental health today target older population with an empathize on dementia and Alzheimer disease.

Year 1-3: MMH patient empowerment tool gives back their voice to the patient. While usually medicine relies on biological activities to determine treatment efficacy, within OPADE study patients are carefully listen and their stories are turned into data.
Year 5: New clinical guidelines with set of biomarkers that help to determine the best anti-depressant and the risk of recurrencies, with the support of the EI-powered predictive tool.
Year 7-10: While the use of OPADE outcomes is used on more and more patients, the AI / ML tool and the biomarker of interested will be investigated for early MDD diagnosis (long term impact after project end) and for other psychiatric diseases.

Economic impact: generating innovation-based growth PBIO, PRO, CEP, AIE, MMH will generate revenues through the commercialisation of the different assets developed and validated during the project.
Year 3: CEP will generate €8M. Year 5: PBIO will generate 9M at market entrance for the identified biomarkers.
Economic impact: create more & better jobs PBIO and PRO will expand central lab capacities in Europe, CEP will commercialise the device and create the needed environment (manufacturing, regulatory, clinical), AIE will commercialise the OPADE AI-predictive tool as a medical device, MMH will extend the service of the company by recruiting head of communities.
Year 1: 6 FTEs created (CEP, PBIO, PRO, AIE), Year 5: 15 FTEs created (CEP, PBIO, PRO, AIE, MMH); Year 7: 30 FTEs created
Economic impact: leveraging investments MMH is currently in discussion with the TOP 5 pharmaceutical companies to include the patient empowerment tool in other clinical trials. CEP, MMH, PRO are currently working to scale-up their businesses. AIE will further raise money for the global commercial launch of the OPADE AI-predictive tool.
Year 1: PBIO close €5M fundraising with EIC support to deploy central labs internationally. Year 3: CEP raise €1M to launch commercialisation at scale. PRO will raise €2-3M to commercialise the MDD biomarker set. Year 5: AIE raise €3-5M to launch the commercialisation of OPADE AI-powered predictive tool.

Potential barriers / risks and mitigation measures

Risk	Mitigation
Regulatory approval (Odds: Low / Impact: Med)	The OPADE AI-predictive tool is regulated by the new in vitro diagnostic regulation (IVDR) that is now the mandatory regulation for all regulated devices newly developed in Europe. The adoption of the regulation has been prepared for years by the competent authorities but OPADE experts are aware that delays are forecast in appointing the notify body. OPADE partners will work experienced RA expert to make sure that the tool gets the CE mark in the best time to reach psychiatrists.
OPADE AI predictive tool obsolescence (Odds: Low / impact: High)	The early obsolescence of the AI-powered predictive tool is mitigated by the smart experimental plan put in place by OPADE consortium. A first bunch of biomarkers are tested to develop the ML module by including the first 100 patients. Every 50 patients the ML module is 'revisited' and biomarkers are selected. If a new biomarker (not in the initial list) is hypothesised as interesting, it will be added to the model.

OPADE proposal is setting barriers for potential competitors:

- Smart data approach: Starting with an unbiased approach will allow the consortium to identify the potential biomarkers of interest in the shortest timeline
- OPADE is generating its proper data set and the availability of the samples in the biobank allows the constant re-analyse of the samples to train the ML / AI tool
- Patients are coming from different parts of the world to ensure that different types of 'microbiome' are considered in the analysis
- The design of the clinical study to include teenagers is breakthrough as drug developers only target adults.
- AIE will adapt its proprietary AI-modeling tool developed and validated with omic samples harvested on cancer patients.

Scale and significance of the project's contribution to the expected outcomes and impacts

OPADE project will reach a relevant scale at the European level. The consortium integrates:

- 17 partners from 12 EU and international countries to track 350 patients over a 2-year follow-up
- Up to 6300 samples (blood, stool, saliva) will be collected over 4 years to be analysed, and that will further be available in EBRIS Biobank for new analysis
- 30 researchers from all levels involved in OPADE to impact the billion of patient suffering from MDD and their families
- 1 clinical guideline that explain the molecular and non-molecular biomarkers to investigate to track anti-depressant efficacy for MDD patients.
- 1 patient profile that correlate EEG, microbiome, immune, genetic, genomic analysis.

OPADE aims at boosting the anti-depressant efficacy by not less than 80% (based on what the preliminary results have shown) and at being able to identify the recurrency in 60-80% of the cases.
By improving the remission to 24% (from 6% today), OPADE AI-predictive tool will contribute to save €28bn yearly in indirect costs.

2.2 Measure to maximise impact – Dissemination, exploitation and communication

Impact pathway methodology

Stakeholder	Outcomes	Impacts
Public and pharma researchers	Understanding of the gut-brain-axis and the biomarkers that play a role in MDD	New molecular targets to extend the understanding of the disease and other psychiatric disorders.
Healthcare professionals (HCPs)	Ability to request appropriate analysis to 1/ optimise anti-depressant efficacy, 2/identify the risk of recurrencies. AI-powered predictive tool available to support decision-making for each physician (hospital settings or not).	Biomarkers that can be used as efficacy biomarkers in clinical studies or the validation of new drugs for psychiatric disorders
General public	Improve the reputation of the anti-depressant efficacy to encourage people in the need for treatment to consult their physicians.	Awareness of the gut brain axis and the involvement in the MDD and other psychiatric disorders
Patients	End the vicious circle to find a suitable treatment based in their profiles.	The correct anti-depressant is identified as the first attempt through the analysis of the omic and immune inflammatory markers. EEG analysis ensure a close follow-up.

Envisaged exploitation activities

Partner	Key activity
MMH	Patient empowerment digital tool to enhance clinical studies
Forecast revenues at 5 years after project end: €	
CEP	EEG wearable (medical device) to monitor patient in real-time
Forecast revenues by 2026: €8.35M	
PBIO	Gut microbiome biomarker for patient stratification and treatment efficacy / control
Forecast revenues at market entrance: €9M	
PRO	
Forecast revenues at 5 years after project end:	
AIE	AI-powered predictive tool to be deployed in clinical practice
Forecast at market entrance €1-1.8M	

Target markets

OPADE is at the interface of several markets. The MDD market is expected to grow from $3.97bn in 2019 to $7.87bn by 2029 (CAGR 7.1%). That includes not only the therapeutic market but also the current treatment practices and medical devices. The global anti-depressant drug market was valued at $15,651M in 2020 and is projected to reach $21,004M by 2030 (CAGR 3.0% 2021-2030). Anti-depressants are among the most frequently prescribed medications. In the US, 12% of the population reported the use of anti-depressant in the last month. With 5 classes of anti-depressants available in psychiatrist drawers, the treatment option easily become a nightmare. The personalised medicine market was valued at $2.21tn in 2021 and is expected to reach over $5.7tn by 2030 (CAGR 11.6%). The healthcare predictive analytics market was valued at $3.74bn in 2019 and is expected to reach $28.77bn by 2027 (CAGR 28/9%).

Patient Journey mapping tool by MMH

In Europe alone, health players spend around €3bn to map patient journeys using doctors interviews and workshops. With MMH technology these costs can decrease by 10x while significantly improving the outcome – using a bottom-up, evidence-based approach that looks at the longitudinal journey of a patient (even outside the clinical setting). Convinced that patients have a role to play in their own health, the patient empowerment tool is developing patient communities to collect and analyse valuable

feedback from the end-user of a drug. MMH will deploy its digital tool within large clinical trials lead by the large pharma industry on chronic diseases. The company is currently in discussion with the top 10 global pharma companies. The tool will give unique insights such as obstacles to treatment adherence directly from the patient to the drug developer, all along the clinical development.

Patient engagement tool by MMH

MMH enables people with chronic disease to discuss with other patients with the same health conditions and improve their quality of life, treatment adherence and acceptance of the disease - while reducing study dropouts. This solution will target a $6.3 billion patient engagement market. A similar approach, based on a peer-to-peer virtual interaction, has already been proven to have a positive impact on patient's quality of life and in turn keep a good patient engagement and minimize the dropout. MMH will keep track of the effects of its tool and prepare the evidence to become a Digital health application (DiGA in Germany).

EEG wearable (medical device) to monitor patient in real-time

Psychiatrists are experiencing an immense challenge. Receiving between 100 to 300 patients per week, they are overloaded, and can only give 45 min per week for a single patient. In addition, European countries experienced the lack of psychiatrists, with for instance 25% of the positions vacant in France. There are in a dire need for a reliable tool to track the 20% of patients that need a constant remote control from home. For a psychiatrist, tracking means understanding patient's emotions change, if there is a risk of relapse between the session, including a risk of suicide and if the prescribed treatment is efficient. The emotion tracking market was valued at €1bn in 2020 and will grow with a CAGR of 10.5% by 2026. Using EEG biosignal from CEP provides the first in kind medical device that allows patient tracking through brainwaves. CEP developed a class IIa medical device that can be positioned on own patient's glasses or directly behind the ears to perform accurate EEG. CEP plans a full market launch in 2024 starting in France by reaching (in the order of interest) independent psychiatrists, private establishment and public hospitals. The company will then reach Belgium, Switzerland and Germany, to finally enter the US market. CEP customer is the psychiatrist who pay €50/model with the access to the AI-powered tracking module. By 2026, CEP forecast to reach 463 private psychiatrists, 145 hospitals to generate 10428 subscriptions associated to €8.35M in revenues.

Metagenomic abundance profiling (MAP) by PBIO

The project will bring the MAP technology into clinical use. The combination of long-range data observed in the MAP analysis together with its cross-kingdom DNA signatures allows PBIO to make unique, multidimensional enterotypes and biomarkers. With the power that will come from amassing very large databases, MAP will be able to link microbiome signatures to specific conditions and therapeutic outcomes in an unprecedented manner. The fact that PBIO can offer this information at low cost and within relevant time dimensions of microbiome modulation shifts will guide patient stratification and therapeutic intervention and maximize the chances of successful outcome for each individual patient, underlying a principle of medicine personalized to the individual and dynamic microbiome. OPADE will serve as a case study, where performance in uncovering the relevant biomarkers is validated, but also benchmarked against state-of-the-art technologies. A detailed view on the time and cost constraints of supporting a clinical program will allow PBIO to refine its business and exploitation strategies, as it targets the enormous market and societal potential of the personalized microbiome theragnostic market. From a commercial point of view, such use of the MAP technology in clinical development, and ultimately true diagnostics and theragnostic, will drive the market adoption of PBIO solutions. Initially, this offering of microbiome dynamics analysis will follow the current centralized services lab model. From one line of operations in Y1, PBIO will grow into 4 lines in year Y3 up to 8 lines in Y5, with capacity to process 20.000 profiles/line annually. A portion of this capacity is targeted to support a number of large longitudinal clinical trials on a global scale. We anticipate a sales price of €50-45/sample for a product that covers sample preparation, metagenomic analysis up to report generation. Prices are minimum 3 times higher on the current market. On a mid-term horizon, PBIO will be developing a portable version of its lab platform with the goal to disseminate the technology and make MAP and microbiome dynamics available in hospitals, pharmaceutical companies and research labs globally, under device/disposable/software revenue model. These devices are currently in development, and are estimated to reach the market in 2025. Based on these assumptions, PBIO may generate €9M at market entrance, and up to €48M in 5 years. We will also consider license fees or 5-10% for analysis in the central lab.

Immune profiling by PRO

Following the OPADE project, PRO will extend the service offer (contractual work). The results will be sold as a fee-based service for research institutions, biotechs and drug developing companies. In case other project partners need to participate in providing the full service, the partners will be paid by PRO who works with the client. We have estimated that the service contractual work based on immunoprofile-microbiome combined biomarker development for MDD, potentially other chronic conditions, will be done in the amount of €300-400,000 per year starting from year 2027. We have estimated that the biomarker licensing fees of OPADE will be €250,000 in 2027. In total, we have estimated that the OPADE project results turnover in 2027 will be in the range of €0,5-0,75M.

AI-powered predictive tool by AIE

The AI-powered predictive tool will be a class C a medical device, regulated by the IVDR (in vitro diagnostic regulation). The interface will be developed to be user-friendly with the physician. It will help to establish patient profiling through simple questions (*ie.* type of treatment), health information (*i.e* age, BMI, diet) and the collection of biomarkers value (*ie* level of IL-6 at M4, cortisol at M1). The AI / ML tool will process the collected data and directly inform the physician on the right anti-depressant, the right dosage and the biomarkers to follow-up during the treatment to prevent recurrency. OPADE partners that will be in charge of the analysis will ensure that results are directly uploaded into the physician interface. At long term, AIE will work with other providers to integrate their results directly.

During the project we will investigate the following business models:

- The AI-predictive tool is sold to pharma companies that will give access to the prescribers (GPs, psychiatrists) for targeted therapies (at market entrance)
- Private clinics that will use it as a marketing advertise on the value their put to improve mental health, targeting hospital's with paediatric services (at market entrance)
- Private schools, very large workplace that have private healthcare service and who promote mental health (at market entrance)
- Healthcare system, but this is a long shoot, as lot of data are needed to prove the value over standard of care (try and see) (after 5 years)

We will propose a monthly subscription per user (€3-5 depending on volume). We estimate that we can reach 10% of the patients with MDD at market entrance (30k patients), generating €1-1.3M in revenues. The adoption if the tool by the healthcare system will drastically boost the clinical adoption and significantly increase our revenues.

Additional revenues coming from pharma companies developing new clinical candidates and looking for a companion diagnostic to be approved with the new drugs.

IPR strategy related to the result type

The patent numbers of the diagnostic tools for depression powered with AI (have a rising trend, especially over the last 3 years. However, the applicants are generally from the USA, Korea, and Canada. So this topic is valuable to work for Europe to generate its own patent portfolio and prevent license dependency.

Table 3 Initial agreement on IP and use rights

Initial agreement on IP & use rights	Contributing	Third parties
Open and FAIR multi-omic data sets on MDD	Open access	
Biobank	Open access	
Clinical guidelines to be generated by the partners	Open access	
MAP platform	IPR	Licensing
MVA platform	IPR	Licensing
CEP device and database	IPR	Licensing
AIE platform	IPR	Licensing
MMH model	IPR	Licensing

Dissemination and use of knowledge generated in the project is governed by the terms of the Grant Agreement and the terms of the Consortium Agreement. In order to make sure that these terms are followed, to avoid disputes and to facilitate business planning, the Steering Committee will maintain an IPR register throughout the lifetime of the project. This document will list all items of knowledge relating to the work of the project (both background know-how and results developed in the project), and make explicit for each item its owner, nature, status and dissemination and protection measures. The directory will be regularly updated and distributed to all partners. It will form a key tool to enable knowledge

management. An initial version of the IPR register will be created at the start of the project. However, at the stage of producing the proposal, the consortium has already considered what kind of strategy should be followed concerning IPR issues for the main results of the project and reached preliminary agreement on this. The basic principle on which we are agreed is that research and development results must be available to a large audience to facilitate wide adoption of project results, while in the meantime having options in place for rewarding those that invested (Table 3). "IPR" mean that the contributing partner will own the IPR of the result that he has contributed to. "Use rights" mean that any third party (licensee) is allowed to request a license to use the IPR generated by another partner (licensor), against a financial compensation to be agreed between the licensor and the licensee.

Possible patenting areas during the project (Table 4)

The consortium envisages to file at least 6 patents and secret know-how in the areas described below. A preliminary freedom to operate analysis confirms that these areas are novel and inventive, not subject to limitations or requirements for third party licensing and have significant potential for further innovation and IPR.

Table 4. Potential patenting area during the project

Domain	Topic and coverage	Lead partner
Artificial intelligence	AI-powered predictive tool	AIE
Process technology	Patient journey mining	MMH
Treatment effect	Treatment effectiveness feedback loop	CEP
Treatment effect	Treatment suggestion system in psychiatry	CEP
Biomarkers	Set of microbiome biomarkers supporting MDD treatment	PBIO
Biomarkers	Immuno-profiling and microbiome associated biomarkers	PRO

Communication and dissemination

Individual dissemination activities

Partner	Specific dissemination, exploitation and communication activities foreseen
EBRIS	2-4 peer-reviewed articles and attendance to 2 conferences per year. EBRIS will disseminate OPADE project results and outcome thought he EBRIS social media network.
CEINGE	Write 5 peer-reviewed articles. Create training course for 10 PhD Students.
EUT	Min. 2 peer-reviewed articles in Q1 journals, present at least 3 poster/oral communication. Use social media channels and webpage aiming at promotion of public / general public awareness. Share knowledge with relevant stakeholders to prepare courses / training on MDD biomarker analysis for students.
PBIO	Participate to 1-2 peer-reviewed articles. Use the OPADE results to demonstrate that the MAP platform is a reliable platform for new customers and convince investors.
AIE	1-2 peer-reviewed articles on AI / ML modelling. Presentation at international congresses.
MMH	Write a peer-reviewed paper for the Business Process Management (BPM) conference on the use of the process mining technology in creating patients' cohorts based on the similarity of their journey.
PRO	Write 3-4 peer-reviewed articles, communicate and engage with the wider public. (e.g. whitepapers, short news in EurekAlert ja ScienceBusiness, ETIS and ERR/Novaator news portals). The findings will also be made available through posting on the institutional websites and social media (@Protobios1, @TalTechKBI) upon publication.
CEP	Write 5 articles in peer-reviewed journals. Organise seminars at the Encéphale and Journée Physchiatrie Neurologie conferences (France), workshop during the European Congress of Physchiatry. Disseminate OPADE results using CEP social media. Reach out stakeholders via patient and psychiatrist associations. Create an online training course for 200 psychiatrists and 300 psychologists, teaching the analysis of EEG during anti-depressant medication.
BIOK	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. Online webinars with key stakeholders (other projects financed by the same call, by calls related to MDD, Public Health, policy makers, etc.) to disseminate project results and move towards a common goal.
FUS	1-2 peer-reviewed articles. 2-3 presentations at international congresses, focusing on non-EU, American audiences.

UNISA	3-5 peer-reviewed articles. 5-6 presentations at international congresses. Training tools for students and the residents in psychiatry specialisation course.
ACC	1-2 peer-reviewed articles. 2-3 presentations at international congresses.
IDIBGI	1-2 peer-reviewed articles. 2-3 presentations at international congresses.
MED	1-2 peer-reviewed articles. 2-3 presentations at international congresses.

Joint communication, dissemination and training activities (Table 5)

The consortium partners will publish 15 to 20 publications by project end. We are targeting the following scientific journals: New England Journal of Medicine, Lancet, JAMA, Annals of internal Medicine, BMJ, World Psychiatry, Annual review of clinical psychology, Clinical Psychology review, Nature, American Journal of Psychiatry, Molecular Psychiatry, Journal of Child Psychology and Psychiatry and Allied Disciplines, Journal of the American Academy of Child and Adolescent Psychiatry, Journal of Affective Disorder, CNS spectrums, Annals of general psychiatry, Journal of Proteome research, Neurotherapeutics.

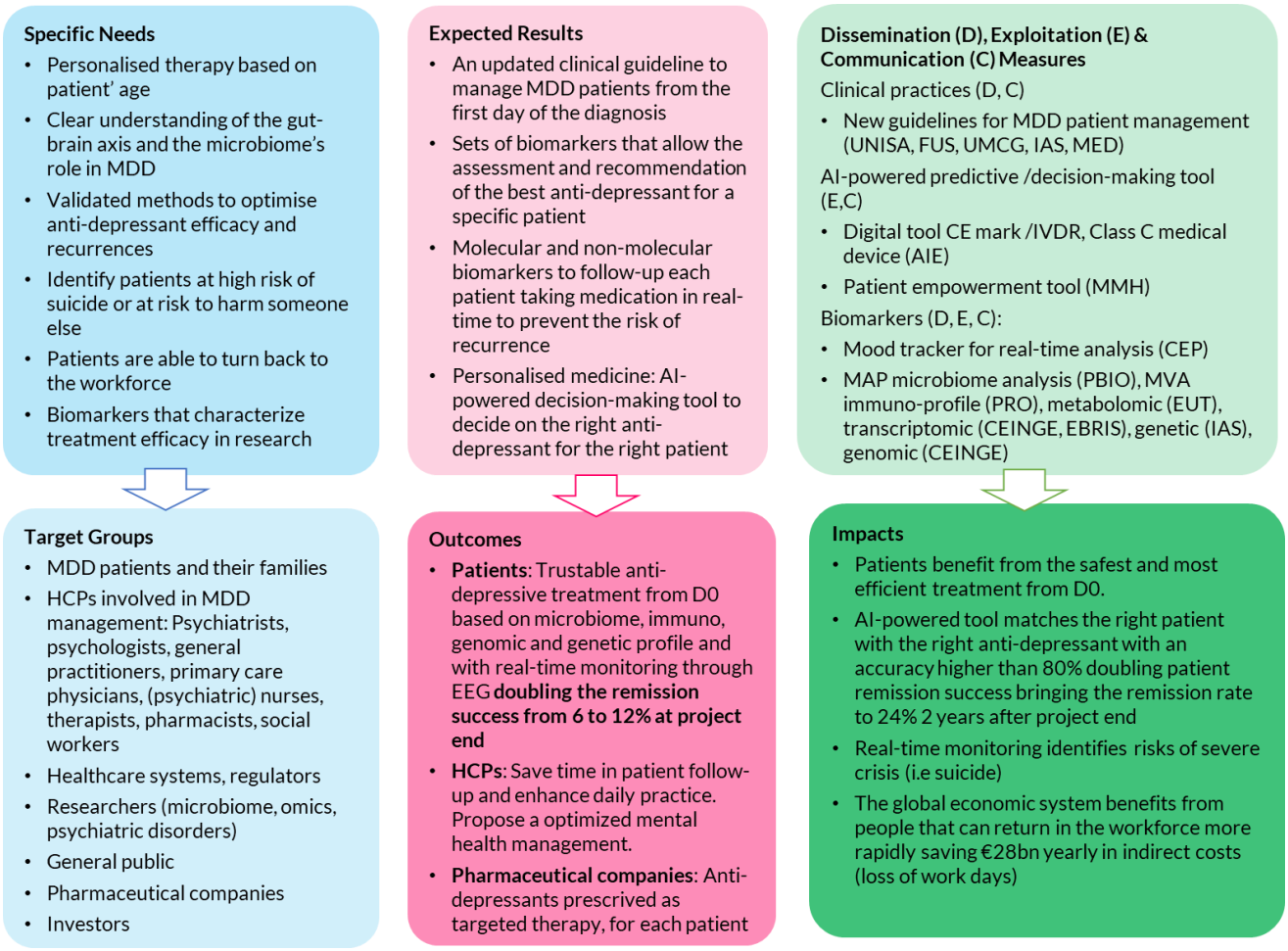
The consortium partners will present the results at international congresses such as WPA world congress of psychiatry, American Psychiatry Association, Child & Adolescent psychopharmacology, Anxiety and depression conference, Euro depression and psychiatry congress, Metabolomics Society, Euro depression and psychiatry congress, Italian Society of Psychopathology, European college of Neuropsychopharmacology.

Several workshops will be organised with projects funded in this call, from other calls related to the MDD, biomarkers cross-cutting priorities (like socio-economic sciences and humanities), as well as other areas of impact of the Destination 5 (Unlocking the full potential of new tools, technologies and digital solutions for a healthy society): 'Good health and high-quality accessible health care' and 'Industrial leadership in key and emerging technologies that work for people'. Events will also be organised with patients who have participated in OPADE and who are or have been involved in other similar projects, giving special prominence to their opinions and contributions, in order to ensure that the advances obtained through research have the best possible impact on the daily lives of the European and South American population. It will also help to ensure that citizens trust and support the opportunities offered by innovative technologies for health care, based on expected health outcomes and potential risks involved.

Table 5. Communication and dissemination KPIs

M14	M28	M40	Year 54	KPI (at project end)
Social media campaign: General public, Patients, patient associations, HCPs, researchers				
Twitter	Twitter LinkedIn	Twitter LinkedIn	Twitter LinkedIn	Twitter followers: 600 LinkedIn group followers: 250
Project videos: General public, Other EU projects				
			1 video	Youtube views: 10,000
Press release: Investors from the OPADE private partners,				
PR #1	PR #2	PR #3	PR #4	Total PR coverage: 2,000
Posters, presentation in congresses, peer-reviewed articles: Researchers in omics, microbiome, depression, HCPs engaged with MDD and / or microbiome, students (R&D, medicine)				
2 posters	3 posters	6 posters	8 posters	Total attendees: 5,000
1 oral com.	3 oral com.	6 oral com.	10 oral com.	Total attendees: 20,000
1 article sub.	2 articles sub.	4 articles sub.	8 articles. Sub	Total readship: 500,000
White papers, non-scientific journal, blog posts: non-experts, general public, patients				
3 articles	7 articles	12 articles	15 articles	Total readship: 30,000
Webinars: patients, patient associations, students, general practitioners				
		Web #1 &# 2	Web #3 & 4	Total attendees: 200
EU cross project opportunities				
	Workshop #1	Workshop #2	Workshop #3	Total attendees: 150

2.3 Summary



3. Quality and efficacy of the implementation

3.1 Work plan and resources

OPADE-MDD is a 54-month project, with the primary goal to develop an AI-powered predictive tool to predict anti-depressant efficacy for a specific patient pattern (targeted medicine) and to optimise anti-depressant efficacy based on multi-omic patient analysis. The total requested budget of the project is €9,997,594. The consortium gathers 14 partners from different member states and associated countries. The total PM allocated is 1138. We defined 4 technical WPs related to the clinical study, patient assessment, sample analysis and development of the predictive tool (WP1-WP4). WP5 is dedicated to the dissemination, communication and exploitation activities, WP6 is dedicated to project management actions and EC interactions.S

Work packages, deliverables, milestones, risks

WP #	WP title	Lead #	Short name	WP leader	PMs	Start	End
WP1	Observational clinical trial management	1	EBRIS	Corrado Vecchi (M)	110	M1	M52
WP2	Cognitive assessment & non molecular biomarkers	8	CEP	Caroline Corrieia (F)	257	M4	M48
WP3	Molecular biomarker quantification	7	PRO	Kaia Palm (F)	393	M4	M53
WP4	Digital tools deployment	6	MMH	Abby Sidibe (F)	232	M4	M54
WP5	Dissemination and communication activities. Exploitation strategies	9	BIOK	Catalina Martinez (F)	79	M1	M54
WP6	Project management	1	EBRIS	Federica carraturo (F)	67	M1	M54
Total PM: 1138 / Total budget: €9,991,656							

Gantt chart

PERT diagram

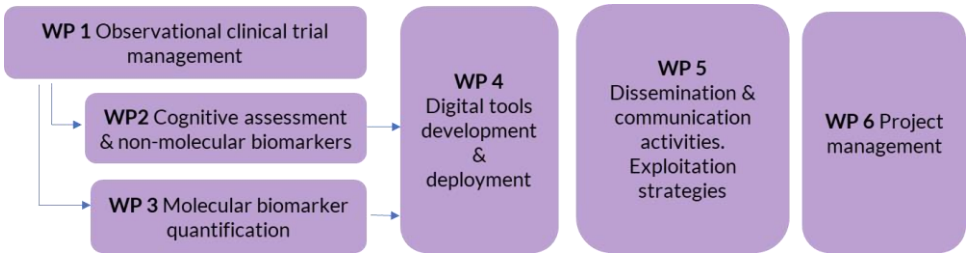


Figure 12. OPADE PERT chart

Work package (WP) description

WP#	1	Lead beneficiary			EBRIS			Start month	M1	End month	M54			
WP title	Observational clinical trial management													
Participant #	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Short name	EBRIS	CEINGE	EUT	PBIO	AIE	MMH	PRO	CEP	BIOK	FUS	UNISA	ACC	IDIBGI	MED
Person-months	60	0	0	0	0	0	0	0	0	10	10	10	10	10
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 of work

Task 1.1: Clinical trial documents preparation and submission (lead: EBRIS, contrib: clinical centres)
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: clinical centres)
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: clinical centres)
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: clinical centres)
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).

Deliverables

D1.1 (T1.1) Documents submitted to competent authorities to initiate the adult and child clinical trials (EBRIS, M4)
D1.2(T1.2) eCRF Validation Report, eCRF Release Report (EBRIS, M5)
D1.3 (T1.3) Mid-term recruitment report (paediatric & adult trials) (EBRIS, M30)
D1.4 (T1.3) Final recruitment report (paediatric and adult trials) (EBRIS, M50)
D1.7 (T1.4) Final Clinical Study Report (adult and paediatric trial) (EBRIS, M54)

WP#	**2**	**Lead beneficiary**		**UNISA /CEP**				**Start month**	**M6**		**End month**			**M48**
WP title		**Cognitive, psychopathological and non molecular biomarkers assessment**												
Participant #		1	2	3	4	5	6	7	8	9	10	11	12	13	14
Short name		EBRIS	CEINGE	EUT	PBIO	AIE	MMH	PRO	CEP	BIOK	FUS	UNISA	ACC	IDIBGI	MED
Person-months		3	0	0	0	10	0	0	45	0	65	100	55	55	60

Objectives

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

Description of work

Task 2.1– Socio-demographic and clinical anamnestic assessment (lead: UNISA, contrib: FUS, ACC, IDIBGI, MED)

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: UNISA, contrib: FUS, ACC, IDIBGI, MED)

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: UNISA, contrib: FUS, ACC, IDIBGI, MED)

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[16]. 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: UNISA, contrib: FUS, ACC, IDIBGI, MED)

[16] *https://ajp.psychiatryonline.org/doi/abs/10.1176/ajp.152.8.1228*

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: CEP, contributors: UNISA, FUS, ACC, IDIBGI, MED)

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.

Deliverables

D2.1 (T2.1) Report on patient socio-demographic and clinical anamnestic assessment (UNISA, M50)
D2.2 (T2.2) Report on patient psychological aspects (UNISA, M50)
D2.3 (T2.3) Report on patient functioning and quality of life (UNISA, M50)
D2.4 (T2.4) Report on patient resistance to treatment (UNISA, M50)
D2.5 (T2.5) Report on patient EEG monitoring (CEP, M50)
D2.6 (All) Global report on non-biological biomarkers (CEP, M52)

WP#	**3**	**Lead beneficiary**		**EBRIS**				**Start month**	**M1**		**End month**		**M54**	
WP title		**Molecular biomarkers quantification**												
Participant #		1	2	3	4	5	6	7	8	9	10	11	12	13	14
Short name		EBRIS	CEINGE	EUT	PBIO	AIE	MMH	PRO	CEP	BIOK	FUS	UNISA	ACC	IDIBGI	MED
Person-months		40	40	72	25	10	0	60	0	0	0	0	0	10	0

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 of work

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: EUT, contrib: UNISA, FUS, ACC, IDIBGI, MED)

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: EUT, contrib: UNISA, FUS, ACC, IDIBGI, MED)

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: EUT, contributors: UNISA, FUS, ACC, IDIBGI, MED)

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 ^{1}H-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: PBIO, contrib: UNISA, FUS, ACC, IDIBGI, MED)

Patient whole gut microbiome analysis will be conducted at multiple points within the study through PBIO 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, UNISA, FUS, ACC, IDIBGI, MED)

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, UNISA, FUS, ACC, IDIBGI, MED)

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, contrib: CEINGE, UNISA, FUS, ACC, IDIBGI, MED)

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: UNISA, FUS, ACC, IDIBGI, MED)

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: PRO, contrib: UNISA, FUS, ACC, IDIBGI, MED)

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, EUT, PBIO, PRO, FUS, UNISA, ACC, IDIBGI, MED)

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, UNISA, ACC, IDIBGI, MED)
- 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 (PBIO, PRO, CEINGE, EBRIS, EUT)

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.

Deliverables

D3.1 (T3.1) Report on analysis of inflammatory markers and growth factors (EUT, M52)
D.3.2 (T3.2) Report on metabolomic analysis (EUT, M52)
D3.3. (T3.3) Report on analysis of lipoprotein profile (EUT, M52)
D3.4 (T3.4) Report on microbiome analysis (PBIO, M52)
D3.5 (T3.5) Report on transcriptomics analysis (EBRIS, M52)
D3.6 (T3.6) Report on epigenomic and genomic analysis (CEINGE, M52)
D3.7 (T3.7) Report on pharmacogenetic and long QT phenotype (IDIBGI, M52)
D3.8 (T3.8) Report on hormonal analysis (EBRIS, M52)
D3.9 (T3.9) Report on immuno-profiling by MVA (PRO, M52)
D3.10 (T3.1-3.9) Report on biological biomarkers (EBRIS, M54)

D3.11 (T3.10) Final repository of the OPADE biobank (EBRIS, M54)

WP#	4	Lead beneficiary		MMH				Start month		M6		End month		M54
WP title		**Development and deployment of digital and tracking tools**												
Participant #		1	2	3	4	5	6	7	8	9	10	11	12	13	14
Short name		EBRIS	CEINGE	EUT	PBIO	AIE	MMH	PRO	CEP	BIOK	FUS	UNISA	ACC	IDIBGI	MED
Person-months		10	4	4	4	120	66	4	5	0	3	3	3	3	3

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 of work

Task 4.1: Deployment of a digital tool for patient community engagement (lead: MMH, contrib, UNISA, ACC, FUS, IDIBGI, MED)

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. MMH 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. MMH 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, MMH 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, MMH 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, EUT, CEINGE, PBIO,PRO)

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 it will have different versions. We will use special DataOPS (Data Operations) techniques/software 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. This means that we will have collected raw data but also generated data.

Task 4.3: Automate the AI-powered data-driven research in the field (lead: AIE, contrib: EBRIS, EUT, PBIO, PRO)

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. The AutoML/AI algorithms inside Python packages like TPOT (http://epistasislab.github.io/tpot/), Pycaret (https://pycaret.org/), Autokeras (https://autokeras.com/), etc., will be applied to the data to develop predictive models. 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. The predictions will be expressed as "If-Then" conditional rules. 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. 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).

Task 4.4: Develop, Implement and Validate the OPADE predictive tools (lead: AIE, contrib: EBRIS, PBIO, EUT, PRO,

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. 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, BIOK)

The complexity of the resulting AI-powered digital tools we develop and clinically validate is reflected in the regulatory roadmap involved. The AIE team will hire a specialized company to 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. Due to the significant impact of our results, and to accelerate the go-to-market process we will also apply for an FDA Breakthrough Device qualification, known to speed up the FDA approval.

Deliverables

D4.1 (T4.1) Final report including set up of the tool and on patient support session (MMH, M50)
D4.2 (T4.2) Report on data integration and validation (AIE, M52)
D4.3 (T4.3) First version on the AI-powered predictive tool (AIE, M30)
D4.4 (T4.4) Report on the development of the AI-powered predictive tool (AIE, M54)
D4.5 (T4.5) Report on the regulatory status of the AI-predictive tool (AIE, M54)

WP#	5	Lead beneficiary		BIOK				Start month	M1	End month		M54	
WP title		**Dissemination and communication activities. Exploitation strategies**											
Participant #		1	2	3	4	5	6	7	8	9	10	11	12	13	14
Short name		EBRIS	CEINGE	EUT	PBIO	AIE	MMH	PRO	CEP	BIOK	FUS	UNISA	ACC	IDIBGI	MED
Person-months		23	1	5	1	1	1	1	1	35	2	2	2	2	2

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 of work

Task 5.1 Communication strategy development (lead: BIOK, contrib: All)

BIOK will identify the best offline and online communication channels to target the audiences pre-defined audiences (regulators, key opinion leaders (KOLs), scientists). BIOK will develop the project branding (website, logo, communication media supports). BIOK will coordinate researcher video interviews and photographic project coverage for promoting the project to the general public, non-governmental organisations and regulator/policy makers. BIOK 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: BIOK, contrib: All)

BIOK 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. BIOK 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: BIOK, 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. BIOK 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: BIOK, contrib: All)

BIOK 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. BIOK 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, BIOK 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: MMH, PRO, CEP, AIE, PBIO)

EBRIS will keep a repository of the exploitable assets identified over 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.

Deliverables
D5.1 (T5.1, T5.2, T5.6) Dissemination, communication and exploitation plan (BIOK, M3) D5.2 (T5.1, T5.2, T5.6) Interim dissemination, communication & exploitation plan 1 (BIOK, M18) D5.3 (T5.1, T5.2, T5.6) Interim dissemination, communication & exploitation plan 2 (BIOK, M40) D5.4 (T5.1, T5.2, T5.6) Final dissemination, communication & exploitation plan (BIOK, M54) D5.5 (T5.3) Clinical guidelines analysis and update (BIOK, M54) D5.4 (T5.4) Report on events with stakeholders (BIOK, M54) D5.5 (T5.6) Report on IPR generated over the project and future exploitation strategy (EBRIS, M54)

WP#	**6**	**Lead beneficiary**		**EBRIS**				**Start month**		**M1**		**End month**		**M54**
WP title		**Project management activities**												
Participant #		1	2	3	4	5	6	7	8	9	10	11	12	13	14
Short name		EBRIS	CEINGE	EUT	PBIO	AIE	MMH	PRO	CEP	BIOK	FUS	UNISA	ACC	IDIBGI	MED
Person-months		54	1	1	1	1	1	1	1	1	1	1	1	1	1

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 of work

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 (see D9.1– D9.5).
- 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 (5 x 52= 52 PMs) has been allocated to EBRIS. All other partners have allocated 1PM to support the reporting of financial information at each of the period and their presence at the periodic reviews.

Deliverables
D6.1 Project quality handbook (EBRIS, M3) D6.2 Data management plan (EBRIS, M3) D6.3 First periodic report (EBRIS, M12) D6.4 Second periodic report (EBRIS, M24) D6.5 Third periodic report (EBRIS, M36) D6.6 Fourth periodic report (EBRIS, M48) D6.7 Final (public) periodic report (EBRIS, M54)

List of deliverables

Table 3.1c. List of deliverables

#	Deliverable name	WP#	Lead	Type[17]	PU	Due
D5.1	Dissemination, communication and exploitation plan	5	BIOK	R	SEN	M3
D6.1	Project quality handbook	6	EBRIS	R	SEN	M3
D6.2	Data management plan	6	EBRIS	R	SEN	M3
D1.1	Documents submitted to competent authorities to initiate the adult and child clinical trials	1	EBRIS	R	SEN	M4
D1.2	eCRF Validation Report, eCRF Release Report	1	EBRIS	R	SEN	M5
D6.3	First periodic report	6	EBRIS	R	SEN	M12
D5.2	Interim dissemination, communication & exploitation plan 1	5	BIOK	R	SEN	M18
D6.4	Second periodic report	6	EBRIS	R	SEN	M24
D1.3	Mid-term recruitment report (paediatric an& adult trials)	1	EBRIS	R	SEN	M30
D4.3	T4.3) First version on the AI-powered predictive tool	4	AIE	R	SEN	M30
D6.5	Third periodic report	6	EBRIS	R	SEN	M36
D5.3	Interim dissemination, communication & exploitation plan 2	5	BIOK	R	SEN	M40
D6.6	Fourth periodic report	6	EBRIS	R	SEN	M48
D1.4	Final recruitment report (paediatric and adult trials)	1	EBRIS	R	SEN	M50
D2.1	Report on patient socio-demographic and clinical anamnestic assessment (UNISA, M50)	2	UNISA	R	SEN	M50
D2.2	Report on patient psychological aspects	2	UNISA	R	SEN	M50
D2.3	Report on patient functioning and quality of life	2	UNISA	R	SEN	M50
D2.4	Report on patient resistance to treatment	2	UNISA	R	SEN	M50
D4.1	Final report including set up of the tool and on patient support session	4	MMH	R	SEN	M50
D2.6	Global report on non-biological biomarkers	2	CEP	R	SEN	M52
D3.1	Report on analysis of inflammatory markers and growth factors	3	EUT	R	SEN	M52
D.3.2	Report on metabolomic analysis	3	EUT	R	SEN	M52
D3.3.	Report on analysis of lipoprotein profile	3	EUT	R	SEN	M52
D3.4	Report on microbiome analysis	3	PBIO	R		M52
D3.5	Report on transcriptomics analysis	3	EBRIS	R		M52
D3.6	Report on epigenomic and genomic analysi	3	CEINGE	R		M52
D3.7	Report on pharmacogenetic and long QT phenotype	3	IDIBGI	R		M52
D3.8	Report on hormonal analysis	3	EBRIS	R		M52
D3.9	Report on immuno-profiling by MVA	3	PRO	R	SEN	M52
D4.2	Report on data integration and validation	4	AIE	R	SEN	M52
D1.7	Final Clinical Study Report (adult and paediatric trial)	1	EBRIS	R	SEN	M54
D3.10	Report on biological biomarkers	3	EBRIS	R	SEN	M54
D3.11	Final repository of the OPADE bioban	3	EBRIS	R	SEN	M54
D4.4	Report on the development of the AI-powered predictive tool	4	AIE	R	SEN	M54
D4.5	Report on the regulatory status of the AI-predictive tool	3	AIE	R	SEN	M54
D5.4	Final dissemination, communication & exploitation plan	5	BIOK	R	SEN	M54
D5.5	Clinical guidelines analysis and update	5	BIOK	R	SEN	M54
D5.4	Report on events with stakeholders	5	BIOK	R	SEN	M54
D5.5	Report on IPR generated over the project and future exploitation strategy	5	EBRIS	R	SEN	M54
D6.7	Final (public) periodic report	6	EBRIS	R	PU	M54

List of milestones

Table 3.1.d List of milestones

#	Milestone name	WPs	Month	Means of verification

[17] R: Document, report (excluding the periodic and final reports), DEM: Demonstrator, pilot, prototype, plan designs, DEC: Websites, patents filing, press & media actions, videos, etc.DATA: Data sets, microdata, etc. DMP: Data management plan ETHICS: Deliverables related to ethics issues. SECURITY: Deliverables related to security issues OTHER: Software, technical diagram, algorithms, models, etc.

MS1	First patient includes in the study (teen or young adult)	1	M7	Report of the visit established by the clinical centre.
MS2	First group of patients integrated in the empowerment digital tool	2	M8	MMH interim research report
MS3	First selection of the key biomarkers is done (80%)	3/4	M18	Research report established by AIE
MS4	First AI-powered patient pattern is presented to the consortium (v1.0)	3/4	M30	Research report established by AIE
MS5	350th patient completed the study	1	M48	Report of the visit established by all the clinical centre
MS6	24-month follow-up on brainwaves performed on 350 patients	2	M48	Report established by CEP
MS7	4 time points for the key biomarkers are done for 350 patients	3	M52	Report on the biological biomarker compiled by EBRIS
MS8	1 new clinical guideline is available to be circulated outside of the consortium	5	M51	Draft document circulated to consortium
MS9	v2.0 OPADE AI-predictive tool is ready to be deployed in clinical practice following appropriate certification	3	M52	Advancement report established by AIE

Key project implementation risks

Table 3.1.e Critical risks for implementation

#	Description	WP involved	Prob 1-10	Severity 1-10	Milestone concerned
R1	Too many patients drop the study before the end of the commitment period	All	3	9	1, 5, 6, 7
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.					
R2	Clinical trial is not complete because of slow recruitment, patient shortage, lack of resources	1, 5	2	7	1, 5, 6, 7
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.					
R3	A research or industrial partner leave the consortium	All	2	6	All
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.					
R4	Delay in regulatory approval for the clinical trials	1,2,3,4	5	6	All
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.					
R5	Biomarker correlation is not conclusive to optimise anti-depressant efficacy for MDD patients	2, 4, 5	2	9	3, 4, 7

We will include a significant number of patients on the study (500) 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 be managed separately. Samples will be kept in EBRIS facilities to run further analysis if needed.					
R6	The identify set up of biomarkers is too expansive to ensure a rapid clinical adoption	2,3	2	6	8
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.					
R7	Data sharing between the partners	All	1	6	
Data sharing will be regulated by the consortium agreement. 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.					

Resources

Summary of staff efforts (Leading partner is indicated in bold)

Table 3.1.f Summary of staff effort

#	Short	WP1	WP2	WP3	WP4	WP5	WP6	Total
1	EBRIS	**60**	3	40	10	23	**54**	190
2	CEINGE	0	0	40	4	1	1	46
3	EUT	0	0	72	4	5	1	82
4	PBIO	0	0	25	4	1	1	31
5	AIE	0	10	10	120	1	1	142
6	MMH	0	0	0	**66**	1	1	68
7	PRO	0	0	**60**	4	1	1	66
8	CEP	0	**45**	0	5	1	1	47
9	BIOK	0	0	0	0	**35**	1	36
10	FUS	10	65	0	3	2	1	83
11	UNISA	10	100	0	3	2	1	118
12	ACC	10	55	0	3	2	1	73
13	IDIBGI	10	55	10	3	2	1	73
14	MED	10	60	0	3	2	1	76
Total		110	393	257	232	79	67	1138

Subcontracting costs

Table 3.1.g subcontracting costs items

N/A – *No subcontracting costs defined within the project. Specific partners have been appointed to perform all the required tests.*

Purchase costs

Table 3.1.h Purchase costs item

EBRIS	Cost	Description
Travel	€45,000	
Equipment	€22,000	2 freezers for biobanking (100% depreciated over 54 months)
Other	€370,500	plasticware + reagents €260k; one shipment per quarter for two years €30k; Project annual meeting organization (logistics, catering, room location etc.), €6.500,00/for year (x5); Travel expenses of #2 stakeholders external to the project invited to the annual meeting each year, @2,000 stakeholder/event (2x5); audit & certificate on financial statement: €3.000,00, dissemination €10,000, FTO analysis €15k

Total	€433,000	
CEINGE	Cost	Description
Travel	€20,000	16 Person trips @€1250
Other	€463,000	plasticware + reagents epigenomic €450k + transcriptomics + Dissemination €10000 + audit €3000
Total	€483,000	
EUT	Cost	Description
Travel	€20,000	16 Person trips @€1250
Other	€334,000	321k consumables + €3000 Audit + Dissemination: €10,000
Total	€354,000	
PBIO	Cost	Description
Travel	€20,000	16 Person trips @€1250
Other	€365,000	€350k stool sample collection, sample treatment, and analysis + €5000 audit + €10000 dissemination
Total	€385,000	
AIE	Cost	Description
Travel	€20,000	16 Person trips @€1250
Other	€39,000	computing €20k + audit €4000 + dissemination €10,000 + discussion with RA consultant for RA strategy €25k
Total	€59,000	
MMH	Cost	Description
Travel	€20,000	16 Person trips @€1250
Other	€127,000	workshop to customize the tool €10k; tool translation in 5 languages €10k; cloud platform infrastructure and support service €10/patient/month=€104k; tech equipment for moderators of patient engagement sessions 3*€3k) + Audit €4000, €10,000 dissemination
Total	€147,000	
PRO	Cost	Description
Travel	€20,000	16 Person trips @€1250
Other	€118,000	consumables €65k + dissemination €10000+audit €3000
Total	€138,000	
CEP	Cost	Description
Travel	€20,000	16 Person trips @€1250
Other	€213,100	consumables for patient headset €152100 + software maintenance €45000+ Dissemination €10000 + audit €6000
Total	€233,100	
BIOK	Cost	Description
Travel	€20,000	16 Person trips @€1250
Other	€20,000	Dissemination related costs: workshops, videos, training materials
Total	€40,000	
FUS	Cost	Description
Travel	€20,000	16 Person trips @€1250
Other	€36,975	consumables clinical trials €600 + €35 cortisol test *65*5+ dissemination €10000 +Shipping to EBRIS €15000
Total	€56,975	
UNISA	Cost	Description
Travel	€31,250	25 person trips @€1,250
Other	€49,975	consumables clinical trials €600 + dissemination €10000 +Shipping to central lab €15000 + Audit 3000 + €35*105*5 cortisol tests + audit 3000
Total	€81,225	
ACC	Cost	Description
Travel	€20,000	16 Person trips @€1250
Other	€36,000	consumables clinical trials €500 + dissemination €10000 +Shipping to central lab €15000 + 60 cortisol tests *5 * €35+3000 audit
Total	€56,000	

IDIBGI	Cost	Description
Travel	€20,000	16 Person trips @€1250
Other	€129,000	genetic test: €350/patients +consumables clinical trials €500 + dissemination €10000 + shipping to central labs €15000 + audit 3000 + 60 cortisol tests
Total	€149,000	
MED	Cost	Description
Travel	€20,000	16 Person trips @€1250
Other	€36,875	consumables clinical trials €500 + dissemination €10000 +Shipping to central lab €15000 + 65 cortisol tests *5 * €35
Total	€56,875	
Total consortium: €2,676,675 in other direct costs		

Table 3.1.i Other costs categories items

N/A

Table 3.1.j in kind contribution provided by third parties

N/A

3.2 Capacity of participants and consortium as a whole

The consortium is multidisciplinary, as shown in the Table 6.

Table 6. Consortium skills

Domains	EBRIS	CEINGE	EUT	PBIO	AIE	MMH	PRO	CEP	BIOK	FUS	UNISA	ACC	IDIBGI	MED
#	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Psychiatry / MMD	X						X	X		X	x	X	X	X
Bioinformatics	X				X		X	X						
Microbiome	X		X	X										
Metabolome	X		X											
Epigenomic		X												
Genetic		X											X	
Immune function	X		X				X							
Biostatistics	X													
AI / ML					X	X		X						
Clinical study	X					X								
Patient network											X	X	X	X
Translational research	X					X		X						
Regulatory affairs / ethics	X							X		X	X	X	X	X
Exploitation	X							X						
Dissemination	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical / digital device			X			X		X						
EU program	X	X	X	X	X		X		X	X	X	X	X	X

OPADE consortium has been set up to achieve the objective defined in the project:
- Establish patient profiles to predict and optimise the efficacy of the treatments prescribed to patients with MDD with an increase in the remission rate and reduction of impairment of real-life functioning.
- Unveil a correlation between neuroinflammatory indices, target indicators of the microbiome, metabolomic, immune-profile linked, epigenomic, enzymatic algorithms with symptomatic MDD pictures
- Identify and evaluate biomarkers that may represent predictive indices of recurrence
- Improve diagnostic accuracy for primary prevention (early biomarkers).
-Evaluate retrospectively - through accurate anamnesis, the onset of depressive symptoms in adolescence.
- Determine to what extent do blood biomarkers correlate with other specific biomarkers

The consortium gathers several academic and private partners experienced in EU projects (EBRIS, CEINGE, EUT, PBIO, AIE, BIOK, FUS, UNISA, ACC, IBIDGI, MED, PRO) that will boost the management

of the project. MMH, CEP young start-ups will benefit from the knowledge learnt during the project to enhance their participation to other EU programs.
OPADE consortium is a women-led company with 83% of the work package leader being women.

Opade	**OPADE: Optimise and predict antidepressant efficacy for people with major depressive disorders using multi-omics analysis**
Essential information to be provided for proposals including clinical trials/studies/investigations/cohorts	

1 Description of the clinical study

1.1 Title, acronym, unique identifier (e.g. EudraCT Number[1], or identifier from ISCRTN[2], ClinicalTrials.gov[3] if available) of the clinical study

OPADE-C: Observational clinical trial to investigate the optimisation of anti-depressant treatment in children with major depression disorders

1.2 Study rationale

Please provide the overall rationale for conducting the proposed study.

Worldwide, depressive disorders are the most prevalent mental health conditions. According to World Health Organization (WHO) estimates, 322 million people worldwide suffer from these disorders (or 4.4% of the world's population), with a higher prevalence in women than men (5.1% and 3.6%, respectively) [WHO 2017]. The prevalence of depressive disorders also varies by age, such as in young adults aged 18-29 years it is about three times higher than in individuals over 60 years old [American Psychiatric Association (APA), 2013]. Depressive disorders occur during adolescence in nearly 50% of cases, and the prevalence in this population is 5%, with high risk of recurrence and chronicity across the lifespan [Malhi and Mann 2018].

Furthermore, from a global perspective, depressive disorders will be the leading cause of disability, measured in years of life with relative burden of disease, by the year 2030 [World Health Organization 2004]. The annual costs of major depressive disorder (MDD) are estimated at $83.1 billion in the United States, with nearly two-thirds due to residual disability [Greenberg et al. 2003]. Socioeconomic factors have been associated with increased prevalence of depression. Understanding this association would improve the clinical management of depression. Buckman et al. (2022) in their systematic review and individual patient data meta-analysis reported that unemployment was associated with a poor prognosis whereas home ownership was associated with improved prognosis, independent of the type of treatment received suggesting that reducing socioeconomic inequalities may improve mental health.

Despite these lifespan consequences, depression can be considered a disorder of youth. Most adults with depressive disorders reported that their first episode occurred during adolescence and prospective studies suggest that onset may be typical in early adolescence [Lewinsohn, Clarke, Seeley & Rohde, 1994].

Pre-adolescent rates of depressive disorders are substantially lower [Bufferd, Dougherty, Carlson, Rose, & Klein, 2012; Harrington, 2002]; with the onset of puberty, the prevalence of the disorder increases with a significant gender imbalance [Merikangas, Nakamura & Kessler, 2009]. Furthermore, adolescent onset confers a particularly high risk of chronic recurrence and impaired functioning throughout the lifespan [Avenevoli et al. 2008; Zisook et al., 2007].

[1] https://www.clinicaltrialsregister.eu/
[2] https://www.isrctn.com/
[3] https://clinicaltrials.gov/

The use of the same diagnostic criteria in adults, children and adolescents denotes that the overlap of the disorder is independent of age. However, there are important etiological differences between adolescent and adult disorder in terms of treatment response and genetic substrate.

Evidence for the efficacy of antidepressants in treating adolescents is poorer than in adult depression; SSRs and tricyclic antidepressants show lower treatment effects than adults [Hazell et al., 1995; Hazell & Mirzaie, 2013; Locher et al., 2017; Thapar et al., 2012]. Taken together, these features of depressive disorder clarify the need for early and effective intervention to treat adolescent depression.

Although several pharmacological therapies are available, there is still significant variability in the response to antidepressant treatment: almost 60% of patients do not recover after a single antidepressant and 20% of these patients do not respond to any intervention [Labermaier C, 2013].

Existing guidelines recommend that initial treatment should be tried for a long period; on average, it takes at least 4 weeks to achieve response and 6 weeks to remission while on treatment with (SSRI), but remission can take 12 weeks or more [Fochtmann and Gelenbe 2005]. However, most patients fail to go into remission with the first prescribed antidepressant [Trivedi et al. 2006] and 42% of these patients stop treatment within the first 30 days [Olfson et al. 2006].

Suitable treatment of major depression could greatly improve the prognosis, increasing the chance of a full return to premorbid levels of functioning [Bauer et al. 2017].

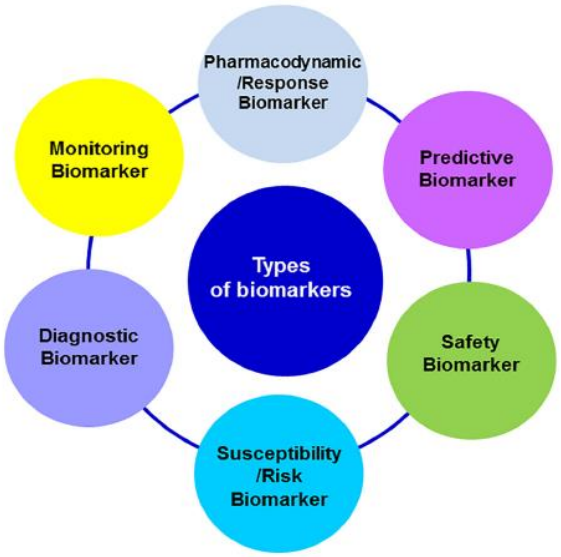
Now, the most effective antidepressant drug for each patient is identified only through a trial-and-error strategy [Dunlop, 2015].

In many cases it takes a considerable amount of time to reach clinical remission, with consequent risk of worsening symptoms and suicidal ideation as well as increased risk of side effects and poor compliance [Leuchter et al., 2009, Zisook 2007].

An increasing number of studies about the treatment of depression have suggested that achieving remission should be viewed as the primary goal [Stahl 1999; Thase 2003]. Many studies have consistently shown that subjects affected by depressive disorders who have responded to treatment but failed to achieve full symptomatic remission continue to have psychosocial impairment and have a higher likelihood of recurrence of a full depressive syndrome [Faravelli et al. 1986; Judd et al. 1998, 2000; Paykel et al 1995].

A challenge regarding the effectiveness of antidepressant treatment is emerging from the integration of personalized medicine into clinical decision making [Insel and Cuthbert 2015]. Indeed, personalized medicine is becoming the challenge of healthcare practice in terms of medical decisions and treatments tailored to the single individual [Snyderman et al. 2012]. It will be able to offer accurate diagnoses and patient-based therapeutic approaches during all phases of the disease, including prevention, diagnosis, prognosis, treatment, and follow-up [Lane et al. 2021]. In this viewpoint, the comprehension of the pathogenetic mechanisms of depression disorders becomes crucial in order to identify possible targets for the treatment. However, although numerous studies have attempted to investigate the interplay of psychological factors with environmental risk factors and biological mechanisms [McIntyre et al., 2014; Lai 2019], the pathways that contribute to the onset of major depressive disorder remain far from elucidated [Wolfer et al. 2019]. This lack of progress is partly attributed to the complexity and clinical heterogeneity of depression, in association with the analytical inconsistency of the literature, which do not allow to identify with sufficiently proven specificity, sensitivity and reproducibility the biomarkers theoretically involved. Biomarkers'

identification is still an ongoing work. A biomarker is defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathophysiological or pharmacological responses to a therapeutic intervention" [Biomarkers Definitions Working Group]. Biomarkers represent a fundamental aspect of modern medicine. They could index the biological processes associated with a disease (diagnostic biomarkers), with the risk of developing a disease, or with the response to treatment or the outcome of a disease (predictive biomarkers). In psychiatry, biomarker research has proven to be more complex than in other medical disciplines [Abi-Dargham and Horga 2016]. For example, it is still debated whether mental disorders should be conceptualized as discrete entities (categorical approach) or as phenomena along a continuum of severity (dimensional approach).



Garcıa-Gutierrez MS, Navarrete F, Sala F, Gasparyan A,vAustrich-Olivares A and Manzanares J (2020) Biomarkers in Psychiatry: Concept, Definition, Types and Relevance to the Clinical Reality. Front. Psychiatry 11:432. doi: 10.3389/fpsyt.2020.00432

It is therefore difficult to identify a reliable and clear demarcation between normal and pathological conditions and between different disorders and the same diagnosis may apply to two individuals who do not have the same symptoms; moreover, more than one mental disorder may be diagnosed in the same individual [Galderisi et al. 2018]. No specific pathophysiological features or biomarkers have been identified for any diagnostic category to date.

Individuals with psychiatric disorders are divided into subgroups based on genetic and clinical characteristics [Lin et al. 2008, 2015; Sadee 2005; Snyderman 2012]. Similarly, treatments could be tailored to individuals with major depression based on previously assessed genetic and clinical biomarkers [Terracciano et al. 2010; Chekroud et al. 2016; Iniesta et al. 2016; Garćıa-Gutierrez et al. 2020]

Based on this, it is important to identify biomarkers that might be able to predict treatment response and ideally biomarkers that can identify the best antidepressant medication for each individual [Patel et al. 2015; Chekroud et al. 2016; Lin et al. 2018].

A primary goal in developing predictive clinical tools is to determine what information should be used.

Imaging studies have demonstrated, through the use of magnetic resonance imaging (MRI) and magnetoencephalography a relevant role of some frontal regions, such as anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC) and orbitofrontal cortex (OFC). In addition, structural and functional alterations in limbic regions, such as the hippocampus and amygdala, could be hypothetical biomarkers for major depression [Lai 2019].

Regarding genetic aspects, genome-wide association studies (GWAS) have been managed to identify susceptible loci that influence antidepressant treatment as a response entity [Lin and Lane 2015]. Similarly, carefully chosen single nucleotide polymorphisms (SNPs) could also be used as genetic biomarkers to predict treatment outcomes and side effects in subjects with major depressive disorder treated with antidepressants [Lin and Lane 2015, Lam et al., 2016, Belzeaux et al., 2017; Cattaneo et al., 2013; Leuchter et al., 2010; Gadad et al., 2017].

Taliaz et al. 2021, using a large patient datasets from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study [Rush et al 2004, 2006; Fava et al. 2003] and the Pharmacogenomic Research Network Antidepressant Medication Pharmacogenomic Study (PGRN-AMPS) [Mrazek et al. 2014] that include genetic, clinical, and demographic data, sought to generate an accurate predictor of response to a panel of antidepressants in order to optimize treatment for MDD using a data-driven approach. The algorithm demonstrates its capabilities of selecting a suitable antidepressant for an individual patient with an average balanced accuracy of 70.1%. However, their algorithm created predictions only for three medications used in STAR*D, whereas clinicians have more therapeutic choices and their data did not include information to detect metabolizer phenotypes' inference.

However, such biomarkers, even if effective, may not be applied on a large scale due to cost, time of collection and processing.

Among all possible biomarkers, peripheral blood and gut microbiome biomarkers represent the most accessible, given their suitability and straightforwardness of collection in clinical practice.

The literature indicates that the markers involved are inflammatory, immunologic, neurotrophic in origin, also involving neurotransmitters, metabolic processes, and neuroendocrine systems (Belzeaux R et al., 2017, Mora et al. 2018). This highlights the need to find quantitative molecular markers to tailor existing treatment strategies to the individual's biological system.

The inflammatory-immune-mediated hypothesis is diagnostically disruptive, because immune dysfunction could contribute to both comorbid depression (associated with clinical inflammation) and MDD in a proportion of individuals who also have laboratory evidence of low-grade inflammation. Immune modulators could alter antidepressant efficacy for people with MDD and biomarker evidence of immune dysfunction related to the targeted pathway, as well as for individuals with comorbid depressive symptoms [Drevets et al.,2022]

The human gut microbiome, sometimes referred to as the second genome, comprises nearly 100 trillion bacteria. A growing number of studies have established that the gut microbiome influences central nervous system development, function and behavior [Cocchi and Gabrielli 2019; Rutsch et al. 2020]. The Microbiota-Intestine-Brain (MGB) axis exerts its effects through immune system activation (e.g., inflammatory cytokines and chemokines), neurotransmitter production (e.g., serotonin, gamma-aminobutyric acid [GABA] and glutamate) and through its metabolites (short-chain fatty acids (SCFA) and key dietary amino acids, such as tryptophan (TRP), while also exerting neuroendocrine functions. Beside influencing specific brain functions, there is now growing evidence that the gut microbiome may also influence the efficacy of several drugs [Wilson et al., 2017)], including antidepressants (Walsh et al., 2018). Therefore, to implement personalized medicine and validate specific biomarkers for population stratification and prediction of drug efficacy, establishing the composition and function of the gut microbiome is becoming a key asset.

Alterations in the microbiota and the resulting inflammatory processes would seem to be implicated in the pathogenesis of mood disorders, particularly MDD [Averina et al. 2020]. This hypothesis is supported, among other things, by the increase in biomarkers of inflammation,

such as cytokines, in the plasma and cerebrospinal fluid of subjects with major depression [Raison et al. 2006; Miller and Raison 2016; Haroon et al. 2012].

Furthermore, this is further supported by the fact that major depression can also develop following cytokine treatment [Haroon et al. 2012]. as well as in the context of numerous medical conditions in which an increased inflammatory component is involved. [Iwata et al. 2013].

For future clinical application in the context of depressive disorders, after the identification in young population of MDD predictors of diagnosis, prognosis, and therapeutic response, the next step would be to integrate relevant measures into tools that could be used in the clinical setting. The development of user-friendly clinical tools that are easy for clinicians without research and statistical backgrounds will drive a key challenge in clinical management [McGuire et al. 2015]. Just as a physician evaluates clinical characteristics in detail to evaluate a subject at high risk for psychiatric pathology or to diagnose a subject with depression, so does the integration of psychopathological characteristics and other neurocognitive, genetic, metabolomic, autoimmune and inflammatory measures, together to MRI scans, it could support the clinic by overcoming the subjectivity of traditional clinical assessments.

1.2.1 Extent and evaluation of current knowledge directly linked to the scientific question(s) to be answered by the clinical study

[insert text]

1.2.1.1 Outcomes (efficacy, safety) of completed and number of ongoing clinical studies utilising the same intervention in the same indication (including review of public registers)

N/A – OPADE is a observational clinical trial

1.2.1.2 Level of evidence related to the mechanism of action of the intervention in the planned clinical study population

N/A – OPADE is a observational clinical trial

1.3 Objective(s) of the clinical study

Please differentiate between primary and secondary objective(s)

In the light of recent findings on the poor effectiveness of antidepressant drugs, the present study, through a prospective investigation, aims to evaluate in adolescent and early adults patients with MDD the presence of specific biomarkers in order to identify the correlation between these indicators and the early clinical manifestations of depression and to investigate their impact on real-life functioning.

Primary objective:

The detection of specific biomarkers in the adolescent and young adults will lead to:

1. the improvement of the effectiveness of the treatment with an increase in the remission rate and the reduction of impairment of real-life functioning

2. the possible correlation between neuroinflammatory indices, target indicators of the microbiome, metabolomics algorithms with symptomatic pictures of depression

3. evaluation of biomarkers that may represent predictive indices of recurrence or replace

Secondary objectives:

4. the discovery of new molecular targets for the personalized approach

5. the detection of new biomarkers can guide the identification of new antidepressant drugs.

6. Improve diagnostic accuracy for primary prevention (early biomarkers).

7. Evaluate retrospectively, through accurate anamnesis, the onset of depressive symptoms in adolescence.

How much and to what extent do blood biomarkers correlate with other specific biomarkers (metabolomic, proteomic, genomic, epigenomic, genetic).

1.4 Characteristics of the study population (size, age group, sex distribution, inclusion and exclusion criteria; all items with justification!)

The study involves four arms divided according to age groups:

- 14-17 years,11 months; 70 patients
- 18-30 years 11 months; 100 patients
- 31-39 years 11 months; 90 patients
- 40-50 years; 90 patients

1.4.1 Details on sample size and power calculation

A sample and statistical analysis plan will be produced for the study before the commencement of the relevant statistical analysis. Sample analysis are processed though AI analysis.

Difference between groups will be performed using 2-way Annova with Bonferroni's multiple comparison test. When data are normally distributed, a one-way Annova will be used with the Kruskal-Wallis test. We will use GraphPad Prism. Results will be considered statistically significant when $p<0.05$.

Microbiome and metabolome data: principle coordinate analysis and distance based redundancy analysis (db-RDA) will be used to explain the (dis)similarity in species composition (using weighted and unweighted UniFrac distances) using the following explanatory variables: treatment, gender and microbiota metabolites levels. The significance of separation in db-RDA will be assessed with the Monte Carlo Permutation Procedure (MCPP). Analyses will be performed using Canoco 5 software for multivariate data exploration. To identify differential abundant taxa from pyrosequencing data, the linear discriminant analysis effect size (LEfSe) method will be applied on taxonomic read abundances. Both treatment and gender will be used as classification in this analysis. Spearman correlations will be applied to associate differential abundant taxa with levels of metabolites, as well as with behaviour scores, immune profile data and neurotransmitter data using add-in XLSTAT developed for Microsoft Excel. Direct comparisons of metabolite levels for treatment and gender will be performed by MannWhitney U tests using software Analyse-it for Microsoft Excel.

1.5 Design of the clinical study (controlled / uncontrolled; randomised; open / blinded; parallel group / cross over / other; please justify the appropriateness of the selected design)

Non-blind, observational, prospective cohort study, cross-sectional study

1.6 Type of intervention (medicinal product / advanced therapy medicinal product / medical device / in vitro diagnostic medical device / surgical or other invasive procedure / other medical intervention, including, e.g., counselling)

Observational, prospective clinical trial

1.7 Description and timing of study procedures

Please provide an overview, preferably in a tabular format, about the schedule of study procedures. Please give a simple statement on how long individual patients or healthy volunteers participate in the clinical study.

MDD patients are enrolled in the OPADE clinical study for 24 months.

Scheduling of the test procedure:

Time	Week	Sample	Biomarkers	Scales	Resistance to treatment
T0	0	Plasma/Saliva/Stool	☑	☑	✕
T1	8	✕	✕	☑	✕
T2	16	Plasma/Saliva/Stool	☑	☑	☑
T3	26	Plasma/Saliva/Stool	☑	☑	✕
T4	52	Plasma/Saliva/Stool	☑	☑	☑
T5	104	Plasma/Saliva/Stool	☑	☑	☑

2 Preparedness status

2.1 Development of the clinical study protocol

Please describe how the below aspects have been or will be addressed in developing the clinical study protocol (if applicable):

2.1.1 Scientific advice from regulatory and health technology assessment bodies

As this is a observational clinical study, there is no need for a scientific advice

2.1.2 Clinical efficacy, safety, and methodological guidelines (including guidelines on statistics)

Prior to the lock of the database and analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the summary set of analyses described below.
Continuous data will be summarized using mean, standard deviation, median, minimum and maximum. Categorical data will be summarized using frequency counts and percentages. Analysis of subject discontinuations and deviations from the study protocol will be defined prospectively prior to data base lock.

2.1.3 Involvement of citizens / patients, carers in drawing up the clinical study protocol

We will deploy MMH patient empowerment tool that will collect patient feedback during the study. We will integrate patient associations at each steps of the discussion.

2.2 Regulatory intelligence to ensure timely regulatory approval and ethics clearance of the clinical study in all jurisdictions where its implementation is planned
Please provide information on the following regulatory and ethics aspects:

2.2.1 How the consortium will ensure access to regulatory expertise necessary to get advice on, and management of, regulatory affairs activities in all concerned jurisdictions?

The documents will be submitted to the competent authorities to receive the approval in each clinical centres. EBRIS will coordinate the discussion with regulatory experts If needed.

2.2.2 How the consortium will ensure access to ethics expertise necessary to get advice on current proceedings and documentation requirements of all concerned ethics committees?

Each clinical centre is experienced in such observational clinical trials and the pathway to obtain the approval for the approval from their ethical committee. EBRIS will coordinate the efforts with external experts if needed.

2.3 How the scientific and operational governance of the clinical study will be ensured?

2.3.1 Please give details about the sponsor(s) (name, type of entity, seat or country of residence).

The sponsor is EBRIS, supported by the European Commission. A steering committee in psychiatry and microbiome will be established since project start. This committee will function in accordance with a Charter produced by the consortium prior to commencing its work.

2.3.2 Please describe the composition, the role and the functioning of the planned board(s), governing bodies.

Our governing bodies - all as approving authorities are:

- Sponsor: EBRIS
- All clinical sites: UNISA, FUS, ACC, IBIDGI, MED
- Clinical trial management: EBRIS

Those different partners will work together to support the efficient delivery of high quality clinical trial services. A well-governed healthcare organisation ensures managers and clinical trial site staff, patients, consumers, clinical trial sponsors and the health service organisation is accountable for their contribution to the delivery of clinical trial services.

They will provide the appropriate staff to support: Finance, Information technology (IT), Human resources, Clinical and non-clinical teams, Clinicians, Site-level trial investigators, Trial managers, Study coordinators, Human Research Ethics Committee (HREC) office, Governance office, Site-specific assessment staff. All actors will be trained and certified according to GCP guidelines.

3 Operational feasibility

3.1 Please describe how the availability of the intervention(s) (including comparators) is secured throughout the entire implementation phase (give details on manufacturing, packaging / labelling operations, storage, logistical, import/export issues, etc.)

N/A

3.2 Please describe how the study population will be recruited
Please give details on the recruitment strategy, monitoring of progress and potential mitigation measures

We will enrol patients diagnosed with MDD. Patients will come at the centre for a planned visit. Based on their fit with the eligibility criteria, they will be offered to join the clinical trial. Each site is committed at project start to recruit a certain number of patients (and budget was defined accordingly).

3.2.1 How many clinical sites will contribute to the recruitment of the study population in which countries? Are these clinical sites part of an established clinical trial network? Please also describe the selection criteria of the clinical sites.

- *UNISA (Italy): consortium of 6 different Italian clinical sites (university of Siena, University of Brescia, University of Perugia, University of Salerno, AOU CItta della Salute e della Scienza Torino)*
- Accare (University medical center Groningen)
- Institut d'Investigació Biomèdica de Girona Dr. Josep Trueta (Spain)
- Medipol (Turkey)

Clinical centres were selected on their expertise in psychiatry, their access to MDD patients and their wiligness to join a EU program.

3.2.2 Will recruitment of the study population be of competitive nature between the clinical sites? (Please describe how underperformance of individual clinical sites in recruitment will be managed.)

Before starting the project, each site has evaluated the recruitment capacities and defined the budget accordingly. The initial plan is set up as below:

		per age group			
	total	14 - 17 Year	18- 30 Year	31-39 Year	40-50 Year
Target	365	73	105	95	92
Italy (UNISA)	105	18	40	20	27
NL (ACC)	60	15	20	10	15
Spain (IBDIGI)	60	20	10	15	15
Colombia (FUS)	75	10	20	25	20
Turkey (MED)	65	10	15	25	15
	total	73	105	95	92

3.2.3 What evidence supports the ability of the individual clinical sites to recruit the required number of study participants within the planned timeline (e.g. documented performance in previous clinical studies of similar complexity targeting very similar study population)?

Each site is linked to academic and/or associated clinical sites so they have access to large potential study sample.

3.3 Please describe what additional supply (e.g. an electronic device for remote data capture, a specific instrument for administering the investigational product, etc.) is necessary to carry out the required study procedures and how this supply will be made available to the clinical sites

Patients will be provided with electronic forms of the questionnaires to be completed. CRF will be made available to all clinical centres (EBRIS lead)

3.4 Please provide plans on data management aspects (data standards, type of data capture, verification of data, central data collection, cleaning, analysis, reporting, security)

At enrolment, patients are pseudonymised though EBRIS system (biobanking, see WP3). Only the referent physician has access to the full name of the patient. Other OPADE partners will only have access to a number that will be used for all the samples.

3.5 Please give details on how reporting obligations (regarding study initiation, safety of study participants, ethical concerns, quality issues, integrity of data, study results) to regulatory bodies and ethics committees will be met.

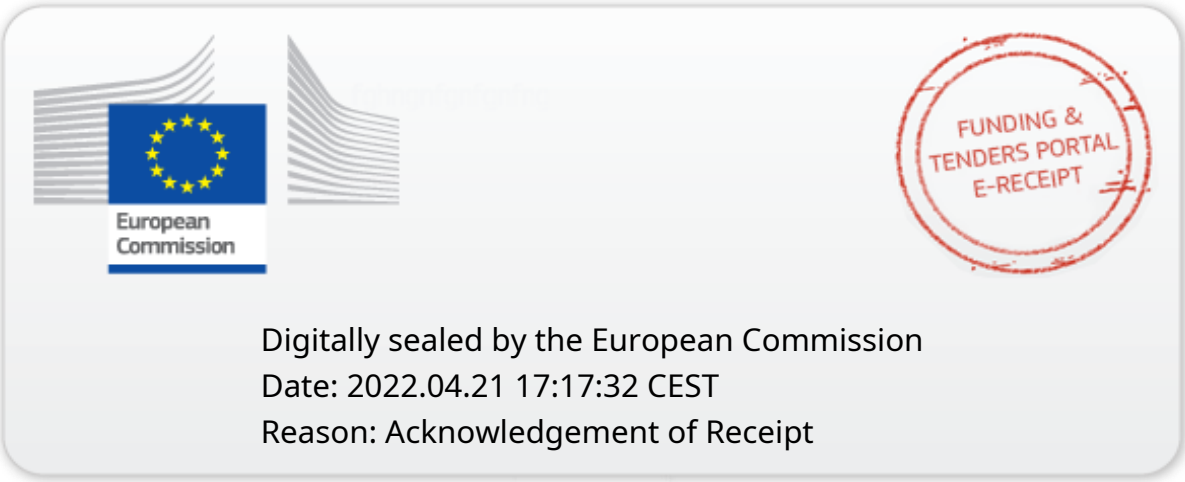
EBRIS will perform quality control checks against source documents. The consortium will verify patient recruitment rate and protocol compliance. They will identify deviations and implement preventive/corrective actions. Project Managers will provide monitoring, review and tracking of monitoring visit at each site from a management point of view.

3.6 Please list all items of the sponsor's responsibilities (e.g. monitoring clinical sites, meeting regulatory obligations, data management, etc.) that will be supported by entities that are not part of the sponsor's organisation. Please describe how the sponsor will ensure oversight of these activities.

LARPASC Partner	**Roles / activities**
EBRIS / sponsor	*Development of study documents*: study synopsis, study protocol, amendments, provide legal representation for EU and non-EU clinical sites *Project management:* Project overview, generate study reports, develop newsletters
Clinical centres (UNISA, ACC, IBDIGI, MED)	*Study activities*: Site setup, data collection, patient recruitment, sample collection, sample shipment to EBRIS biobank.

3.7 What are the plans for major study milestones and what evidence supports its feasibility? Please describe a realistic plan (based on prior experience) detailing the time necessary for (i) compiling the required regulatory and ethics submission package, (ii) receipt of regulatory and ethics approval, (iii) initiation of clinical site(s), (iv) completion of recruitment of the study population, (v) final assessment of all study participants, (vi) analysis and reporting of the study results.

M3: Submit all the request to the ethical committee to get approval
M6: Approval from the ethical committees to start patient enrollement
M6 to M48: Patient enrollement with 24-month follow-up (6 visits)
M48 to M54: Final clinical report and study closure.



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