Horizon 2020 Project LETHE

"A personalized prediction and intervention model for early detection and reduction of risk factors causing dementia, based on AI and distributed Machine Learning."

Research and Innovation Action

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Document information and history

Deliverable description (from DoA)
This deliverable will describe all the ethics and related legal aspects relevant to the project, the associated actions and responsibilities already in place and to be implemented in the Data Management Plan and will assess the impact in terms of fundamental rights, data protection, and privacy of the methods proposed in the context of the project.

Please refer to the Project Quality Handbook for guidance on the review process and the release numbering scheme used in the project.

Release number	Release date	Author [Person and Organisation]	Milestone*	Release description /changes made
V. 0.1	11/04/2022	Patrizia Mecocci (UPG)	TOC	Privacy Monitoring Framework defined
V.0.2	24/05/2022	Patrizia Mecocci (UPG)	Intermediate	Update of ICF mudules
V.0.3	16/06/2022	Patrizia Mecocci (UPG)	Pre-final	Definition of Annexes
V.0.4	27/06/2022	Patrizia Mecocci (UPG)	Final	Implementation of comments and finalization
v.0.5	29/06/2022	Matteo Colombo (i2G)	revised	

** The project uses a multi-stage internal review and release process with defined milestones. Milestone names include abbreviations/terms as follows:*

- *TOC =" Table of Contents" (describes planned contents of different sections);*
- *Intermediate: Document is approximately 50% complete – review checkpoint;*
- *ER = "External Release" (i.e. to commission and reviewers);*
- *Proposed: document authors submit for internal review;*
- *Revised: document authors produce a new version in response to internal reviewer comments*
- *Approved: Internal project reviewers accept the document.*

Table of Contents

1 Executive Summary

The current document and the following updates to be released during the project lifespan describe the annexes developed for the privacy issues management of all the actors involved in the project and its ethical and legal implications. In addition, the next D6.4 version, expected in month 42, will report the results of the implementation of the framework defined and tools proposed in the current document, as well as additional annexes required during the project implementation and the possible future amendment of the consent forms.

The document defines a privacy monitoring framework relevant for the LETHE project's compliance with the GDPR since the project will obtain, use and store personal data relating to project participants. In addition, the document includes sections describing the data protection policy, the data subjects' rights, the pseudonymization procedure, and the data breach recovery plan.

Finally, the document includes specific annexes used as template forms by LETHE clinical centers during the pilot trial phase.

2 About this Document

UPG drew up this deliverable with the contribution of the partners i2G and THL.

The objective is to ensure compliance with the "ethics requirements" related to the guidelines of the Horizon 2020 project.

This document is public as it describes detailed information about ethics and related legal aspects relevant to the privacy issues management of all the actors involved in the project.

The purpose of this document is to clearly define the application and explanation of the European Regulation on the Protection of Personal Data (EU GDPR) in the informed consent form and privacy sheet for the subject involved in the Lethe project. The document includes sections describing the data protection policy, the data processing legal bases, and the data subjects' rights.

2.1 Role of deliverable

The information reported in this deliverable is the result of the work carried out in collaboration with other tasks of the work packages strictly related to this:

Work package 6: Task 6.1 Data management [M1-M42]; Task 6.2 Ensure the availability of compliance data [M12-M42].

Work package 7: Task 7.1 Preparation of the study protocol [M1-M12]; Task 7.2 Preparation for the approval of the Ethics Committee [M12-M18].

This action was being performed through regular meetings between the representatives of the clinical centers and other project partners on MS Teams and through the sharing of the various documents in Sharepoint, such as versions of the study protocol, joint data protection agreement, joint data controller, Informed Consent Form, and privacy sheet to allow all the parties involved to read, suggest modification and comment.

2.2 Relationship to other LETHE deliverables

D10.1 [M6]: H Requirement n.1 of the LETHE project covers the procedures to be applied to relevant project activities for compliance with ethical requirements related to the guidelines of Horizon 2020 projects (responsible partner: UPG).

D10.2 [M6]: POPD - Requirement No. 2 (responsible partner: INFO).

D6.1 [M6]: Data Management plan and ORDP I (responsible partner: INFO).

D7.1 [M12]: Study protocol, description of the detailed study protocol (responsible partner: THL).

D7.2 [M18]: Ethical Committee approval, Ethical approvals from all four evaluation study sides (responsible partners: MUW).

D8.8 [M18]: Recommendations on social and ethical implications of the project (responsible partner: AE).

2.3 Structure of the document

Deliverable 6.3 – Privacy and legal framework I of the LETHE project.

The following points have been analyzed in this deliverable:

. Ethical standards and guidelines of Horizon 2020

. Data Protection Policy adopted in the pilot trial phase

. LETHE Informed consent Form (ICF)

Finally, the document includes specific annexes to support the privacy monitoring activities and a template of the consent form to be translated into the native languages of each clinical center.

3 Ethical standards and guidelines of Horizon 2020

The members of the Consortium, as previously written in D10.1 (M6), declare that the LETHE study conforms to current legislation and regulations in the countries where the research will be carried out. This implies that the Consortium respects people, human dignity, and fair distribution of the benefits and burden of research and protects the research participants' values, rights, and interests. Moreover, the LETHE study conforms to relevant EU legislation such as the Charter of Fundamental Rights of the EU, the Declaration of Helsinki (World Medical Association - Declaration of Helsinki), the latest version, Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and the free movement of such data", Directive 2002/58/EC "processing of personal data and the protection of privacy in the electronic communications sector." Nothing in the proposal conflicts with the opinions of the European Group of Advisers on the Ethical Implications of Biotechnology (1991-1997) and the opinions of the European Group on Ethics in Science and New Technologies (as from 1998). Ethical committee approval for the LETHE trial will be obtained in each country before carrying out the trial. No trial will be performed without checking approval by the ethical committee and data protection authorities of the respective countries.

In addition, each clinical center, by signing a “LETHE INVESTIGATOR SIGNATURE SHEET” **(ANNEX 1),** formally undertakes to conduct this study in accordance with the study protocol and according with the ethical standards and guidelines of Horizon 2020, including the Charter of Fundamental Rights of the European Union and the European Convention on Human Right. Medical research in human subjects will follow the procedures described in the World Medical Association's Declaration of Helsinki and the Oviedo Bioethics Convention (Convention on Human Rights and Biomedicine). In addition, all procedures will comply with National law and the European Union’s General Data Protection Regulation (GDPR). Relative procedures will follow the ICH Guidelines for Good Clinical Practice E6(R2) and the Good Clinical Practice Directive 2005/28/EC.

3.1 Site Team and site staff training

Each clinical center will keep a register of the staff involved in the study and authorized to come into contact with the data of the subjects and with the procedures of the protocol **(ANNEX 2)**; this will help the PIs of the individual centers always to keep track of the authorized persons present on the site and minimize the risk of unauthorized persons coming into contact with the data collected in the trial.

In addition, as required by the protocol (version 1.1 of 22/06/2022): " All assessors will be required to have received formal training in the relevant field (multidisciplinary team including a nurse, a physician, a psychologist, a physiotherapist, and a nutritionist/dietitian) and they will also receive study-specific training (1 day to 2 weeks depending on the task). All study personnel conducting tests will be trained (...) "; to guarantee these training and updating standards, a log **(ANNEX 3)** has been created in which all the training that the site staff will follow before the start of the trial will be traced. The log shows the date and the topics of the training, the modality (face to face, self-read, telephone, online, etc.), the trained person, and the trainer.

3.2 Considerations About Informed Consent (IC)

An essential condition for acquiring a person's Informed Consent to participate in clinical research is the satisfaction of the scientific and ethical rigor principles.

With regard to ethical principles and their application to the IC the following must be taken into particular consideration:

- the principle of respect for the dignity of the person;

- the principle of respecting the right to self-determination of the competent subjects involved in the trial;

- the fairness of the risk/benefit ratio

It is important that the request for consent and the information documents are formulated in such a way as to guarantee absolute compliance and application of the principles that inspire the practice of IC so that the subject is led to be aware that he is not passively undergoing the experiment, but that he voluntarily decides to participate in it.

The IC and the patient information form tend to guarantee the alliance or therapeutic agreement between doctor/investigator and patient; they should take a formulation that explicitly declares and specifies the positions of the subjects in question, their respective obligations, and rights, commitments, and waivered required and expected. From an ethical and deontological point of view, these aspects do not have a value. They are only theoretical, but they imply a practical commitment in the doctor / patient relationship context. These preliminary considerations are inspired in particular by the paragraph “Informed Consent, Special Communication: arts. 25-32 "of the Declaration of Helsinki (D.H.: World Medical Association Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects) to which a series of clearly expressed and shared criteria are reported. Specifically, art. 22. of the D.H. reads: “The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects, and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions. " Here, it implicitly refers to the following ethical principles explained explicitly in other articles:

- the duty of the doctor/investigator to safeguard the health, well-being, and rights of the patient (D.H., art.4);
- the commitment of the doctor/investigator to protect life, health, dignity, integrity, right to self-determination, privacy, and confidentiality, as well as the affirmation that the responsibility for the protection of research subjects always lies with the doctor or health professionals and never of the research subjects (D.H., art.9);
- the duties regarding the scientific and technical standards with which the research is conducted (D.H., articles 12 and 21);
- the patient's right not to participate in the experimental project or to withdraw from it, at any time, without risking any form of retaliation (D.H., art.26).

The informed consent is documented using a written form, signed and personally dated by the subject and by the experimenter doctor/investigator who provided the relative information. The form must comply with the principles of Helsinki, drawn up in compliance with the "good clinical practice," assessed and approved

by the independent ethical committee. The text of the IC can be modified during the study following an amendment every time there is new information about the study protocol. The changes must be approved by the Ethical Committee, and the person involved must be informed of it and must sign the new consent. The subject has the right to withdraw his/her consent during the study at any time.

In any case, the offer of a written consent form may replace the personalized interview.

For this purpose, it is advisable to carry out the interview in a comfortable environment and in a relaxed and serene atmosphere, aiming to comprehensively inform the participant in an effective and efficient way, avoiding information overload. Criteria of exhaustiveness, conciseness, cost-effectiveness, efficiency, and effectiveness, aimed at preventing information overload, are particularly relevant in drafting the form of information that the participant will have to read and subscribe to.

Before granting one's consent, the subject must have the time necessary to inquire about the details of the experimentation, reflect and decide without any pressure or constraint. In fact, there is talk of the process of informed consensus that is marked several times:

1. First meeting with the reference doctor of the study in which the clinical study illustrates and dialogues with the person involved so that the experimentation is understood. The doctor/investigator provides the documents and illustrates all aspects in detail: Module of informed consent, in its two substantially related sections i.e., Information section relating to the protocol and the rights of the person; Section for the expression of consent; Authorization to the processing of personal and sensitive data, as ordered by the privacy law (Legislative Decree no. 196/2003, and subsequent amendments);
2. Time to reflect in which the person involved has the opportunity to carefully read the information received from the doctor/investigator, to confront third parties, family members, and friends, with their doctor.
3. If the subject agrees to participate in the study, he/she is asked to date and sign the informed consent at the doctor office. A copy of this document is delivered to the patient.
4. Willing to confront and talk to the patient during the study continuously and on the basis of the planned phases. In fact, informed consent is a continuous information process that takes place throughout the clinical study, including the follow-up period, and is not an impromptu act.

The art. 26 of the D.H: “In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject’s freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed. All medical research subjects should be given the option of being informed about the general outcome and results of the study”.

3.3 Difference between INFORMED CONSENT and PRIVACY CONSENT

In the field of scientific research, it is essential to manage the risk of overlap between:

- Informed consent of participants in research projects involving humans
- Consent to the processing of their personal data (so-called "privacy consent")

The differences are both conceptual and operational, and also the "Preliminary Opinion on Data Protection and Scientific Research" of the European Data Protection Supervisor (EDPS) urges not to consider them as a single and indivisible requirement. The privacy consent does not concern the research project as a whole, but the processing of the participant's personal data (so-called "interested") that the data controller (investigator center, pharmaceutical company, or medical device company who holds the role of promoter/sponsor, etc.) carried out in the context of a clinical study.

The GDPR defines consent to the processing of personal data as an "Unequivocal positive act by which the interested party expresses the free, specific, informed and unequivocal intention to accept the processing of personal data concerning him [...]".

As far as the interaction between the General Data Protection Regulation 2016/679 (GDPR), which entered into force on 25 May 2018, and the Regulation 536/2014 on clinical trials (CTR), that will be coming into full effect in 2022 and replace the Clinical Trials Directive (2001/20/EC), it's important to underline that the GDPR guarantees the protection of individuals with regard to the processing of personal data and harmonized rules on the free circulation of such data, the CTR aims to ensure greater harmonization of the rules on the conduct of clinical trials across the EU. These two regulations apply simultaneously, and that the CTR constitutes a sectoral regulation that includes specific provisions relevant from the point of view of data protection and does not derogate from the GDPR.

In the difference between IC pursuant to the regulation on clinical trials and consent pursuant to the GDPR lies a possible misunderstanding that the LETHE consortium wanted to clarify:

- The requirement of IC by the CTR must not be confused with the privacy consent as a legal reason for the processing of personal data referred to in Article 6, paragraph 1, letter a) of the GDPR.
- The IC required by The Clinical Trials Regulation serves as an ethical standard and procedural obligation. IC under the CTR is the basic condition under which a person can be included in a clinical trial. It is not intended as a tool for compliance with data processing.

With regard to the legal basis under the GDPR, the various processing operations involving the use of data relating to clinical trials, which include both research-related operations and operations necessary for the protection of health or carried out in the public interest, may be based on a different legal basis. It will be up to the controller to assess and implement the most appropriate legal basis. The consent to the processing of personal data, on the other hand, must be free, specific, informed, and unequivocal as well as explicit for the processing of particular data (e.g., those relating to the health of the person concerned).

4 Data Protection Policy

The purpose of the data processing for the data controllers and data on behalf of the data controller is:

"Develop a digital workspace/repository allowing consortium partners to store and share their datasets (data from the LETHE pilot trial) in a centralized and secure environment, facilitating collaboration and further research development through synergies. The ultimate objective is to utilise the workspace/repository for a personalized prediction and intervention model for early detection and reduction of risk factors causing dementia, based on AI and distributed Machine Learning."

Develop a secure, FAIR-by-design repository allowing storage/sharing of different data types and formats from heterogeneous sources. This will enable data to curation and preservation for future use beyond the project when this is decided and defined.

For better sharing, integration, and use of data in order to achieve the Work Package-specific objectives of the project, the LETHE Repository will become functional and potentially under certification. Data sharing agreements will be agreed upon and signed by the consortium partners.

4.1 Joint data controller agreement

"Data Controller" shall mean an entity that alone or jointly with others determines the purposes and means of the Processing of Personal Data.

In this phase 2 of the LETHE project, aiming at performing the research using the data collected in the pilot trial, the Data Controller are:

- Medizinische Universität Wien (MUW), Spitalgasse 23, A-1090 Vienna, Austria
- Universita degli Studi di Perugia (UPG), Piazza dell'Università 1, IT-06123 Perugia, Italy
- Karolinska Institutet (KI), Department of Neurobiology, Care Science and Society (org. no. 202100-2973), Department Management, level 3, section D Alfred Nobels Allé 23, 23400, SE-141 83 Huddinge, Sweden
- Finnish Institute for Health and Welfare (THL), Mannerheimintie 166, FI-00271 Helsinki, Finland
- FH JOANNEUM Gesellschaft mbH (FHJ), Institute of eHealth, Alte Poststraße 149, A-8020 Graz, Austria
- Combinostics Oy (COMB), Hatanpään Valtatie 24, Tampere 33100, Finland

All data controllers will sign a joint controller agreement before data collection begins, accepting to be responsible for the lawfulness of processing personal data in the context of the study. The agreement determines the Data Controllers' respective responsibilities for compliance with the obligations under the GDPR, in particular regarding exercising the rights of the data subject and their respective duties to provide the information referred to in Articles 13 and 14 of the GDPR.

For more information, consult the "Joint data controller agreement (JDCA)" produced by INFOTREND in the context of WP6 - Data Protection and Ethical Impact; T6.1 "Data Management", *in progress*.

4.2 Data processor agreement

"Data Processor", shall mean an entity that Processes Personal Data on behalf of one or more of the Data Controllers.

"Process" or "Processing" shall mean any operation performed on Personal Data, whether or not by automated means, such as collection, organization, structuring, storage, use, dissemination, or otherwise making available, erasure or destruction.

In this phase 2 of the LETHE project, aiming at performing the research using the data collected in the pilot trial, the Data Processors are:

- Extra Red Srl (ER), Via Salvo D'Acquisto 40/P, Pontedera 56025, Italy
- Infotrend Innovations Company Limited (INFO), Demonaktos Street 13, Lefkosia 1017, Cyprus
- Idryma Technologias Kai Erevnas (FORTH), N Plastira Str 100, Irakleio 70013, Greece
- EGI Foundation (EGI), Science Park 140, 1098 XG Amsterdam, Netherlands

All Data processors will sign a data processing agreement before the data collecting begins between the data controller to ensure that personal data is not processed illegally, wrongfully, or processed in a way that results in unauthorized access, alteration, erasure, damage, loss, or unavailability. The agreement governs the data processor's processing of personal data on behalf of the data controller, including collection, registration, compilation, storage, disclosure, or combinations of these, in connection with the use of/processing in Project LETHE (λήθη) Digital Cognitive Biomarkers, Phase 2. For more information about which types of personal data each processor will be processing and other information about the agreement, consult the "DATA CONTROLLERS – DATA PROCESSORS AGREEMENT" produced by INFOTREND in the context of WP6 - Data Protection and Ethical Impact; T6.1 "Data Management," *in progress*.

4.2.1 Sub-processors

"Subprocessor", shall mean any processor which a Data Processor engages to carry out specific Processing activities on behalf of any of the Data Controllers.

The data processor is obliged to enter into separate agreements with sub-processors that govern the sub-processor's processing of personal data in connection with the data processing agreement. Therefore, the data controller, before the data collection begins, will approve that the data processor contracts the following sub-processors to satisfy this agreement:

- Subprocessor for EGI Foundation: IPHC / SCIGNE Platform.
- Fitbit (FB), 199 Fremont St, San Francisco, CA 94105, USA
- Kaasa Solution GmbH (KA), Friedenstraße 51, 40219 Düsseldorf, Germany
- Google LLC, 1600 Amphitheatre Parkway in Mountain View, California, USA

For more information about which types of data each sub-processor is processing and other information about the agreement, consult the "DATA CONTROLLERS – DATA PROCESSORS AGREEMENT" produced by INFOTREND in the context of WP6 - Data Protection and Ethical Impact; T6.1 "Data Management", *in progress*.

4.3 Pseudonymization Policy

At the base of the pseudonymization there is the individual and his identity; therefore, pseudonymized data are still considered ‘’personal data’’ and, therefore, under the rules of GDPR.

Pseudonymisation is the process by which an individual is prevented from being identified through his/her data.

GDPR defines ‘’pseudonymization’’, Art.4(5), as “the processing of personal data in such a way that the data can no longer be attributed to a specific data subject without the use of additional information, as long as such additional information is kept separately and subject to technical and organizational measures to ensure non -attribution to an identified or identifiable person”.

GDPR in recital 26 tries to provide an explanation about the application of this measure: "The application of pseudonymisation to personal data can reduce the risks for data subjects and help data controllers and processors to comply with their data protection obligations. The explicit introduction of "pseudonymisation" in this regulation is therefore not intended to preclude other data protection measures ".

For Art. 32 GDPR: (...) the data controller and the data processor implement adequate technical and organizational measures to ensure a level of security appropriate to the risk, which includes, among others, where applicable: pseudonymisation and encryption of personal data; (...)

For the pseudo-anonymization process of the data that will be collected during the study, the LETHE consortium has decided that each subject will be provided with a "subject code" identification code upon entry into the study and a dummy Google account that does not contain identification data.

Study data will refer to the subject using the "subject code". The subject's name and contact details will never be made public and will be kept separately from the ID codes in a secure place with limited access to the clinical center staff involved in the study. Only the following people will be able to connect the code to the identity of the subjects at the study center:

- The study doctor and the people with whom he collaborates at the experimental center for the purpose of conducting the study.

- Authorized representatives of the office of the study held to secrecy, as well as representatives of the national and/or foreign health authorities and of the related ethics committees, can view such data to the extent that this is necessary or prescribed to verify the proper conduct of the study.

For this reason, it will not be possible to guarantee absolute secrecy. In the unlikely event that security is compromised and the personal data of one or more individuals become available, we will inform the data subjects, the data protection authority, and all data controllers of the lawfulness of personal data protection.

4.4 Personal data breaches

A personal data breach means an event leading to the destruction, loss, alteration, or unauthorized disclosure of or access to, personal data.

Examples of personal data breaches include lost data transfer devices, such as USB memory sticks, stolen computers; hacking; malware infection; cyber-attacks; fire in the data center, and mailing a bank statement

to the wrong person. Both the controller and processor of personal data must protect the data with security measures corresponding to the risk related to the processing of personal data.

The controller must also prepare for possible personal data breaches by drawing up guidelines for the eventuality of personal data breaches and be able to react to personal data breaches as quickly as possible.

The controller must assess the level of risk caused by personal data breaches to the individuals concerned, for example, no risk; risk; high risk. The 'high risk' means the threshold for notifying individuals is higher than for reporting the relevant supervisory authority.

A personal data breach can have consequences such as loss of control over personal data, identity theft or fraud, damage to reputation, or the reversal of pseudonymisation or loss of confidentiality of personal data. The level of risk determines the measures required from the controller. Such actions can include:

• documentation of the personal data breach

• notification to the supervisory authority

• notification to the data subjects

There is an obligation to document all personal data breaches, their effects and corrective actions taken, regardless of any measures required by the personal data breach. Failure to comply with the documentation or notification obligations constitutes a violation of the General Data Protection Regulation (GDPR) and may result in the sanctions specified therein.

• **Data Breach Notification to the Data Subjects–ANNEX 4** - the document to be used in case of a data breach

• **Data Breach Register –ANNEX 5** - Project's Internal register of data breaches communicated by partners' data controllers

As is explicitly stated in the JDCA:

"MUW, UPG, KI, THL, FHJ and COMB are responsible for compliance with Article 33 of the GDPR, that is, within 72 hours on notification of a personal data breach to the supervisory authority concerning the Personal Data they provide.

MUW, UPG, KI, THL and FHJ and COMB are responsible for compliance with Article 34 of the GDPR on communication of a personal data breach to the Data Subject concerning the Personal Data they provide.

After having become aware of a personal data breach, within 36 hours, a Data Controller must inform the other Data Controllers of the breach. The Parties agree to provide reasonable assistance as is necessary to each other to facilitate the handling of any data breach in an expeditious and compliant manner".

The contact details of the Data Protection Officer to be contacted are the following:

Lelia Ataliani | Email: lelia@infotrendco.com

Infotrend Innovations Co Ltd

13 Demonaktos str. 1017 Nicosia- Cyprus

Mobile:00-357-99-627600

4.5 Principles of the data protection

The data protection principles must always be observed when processing personal data and must be adhered to for the entire duration of processing.

The data-protection principles state that personal data must be:

- processed lawfully, fairly, and in a transparent manner about the data subject;
- collected and processed for a specific and lawful purpose;
- collected only to the amount necessary for the processing;
- updated when required – inaccurate personal data must be erased or rectified without delay;
- kept in a form that only permits the identification of data subjects for as long as is necessary for processing the personal data;
- processed confidentially and securely.

4.6 Legal bases for the data processing

Processing is necessary to pursue the legitimate interest of the data controller (Article 6, paragraph 1, letter e), in conjunction with Article 9, paragraph 2, letter i) or j), GDPR.

The CTR provides that the processing of personal data may be "necessary for the pursuit of the legitimate interest of the data controller, provided that the interests or fundamental rights and freedoms of the data subject do not prevail" - under Article 6, paragraph 1, letter e), of the GDPR. However, for the processing of particular categories of data, the legal basis referred to in Article 6 of the GDPR applies only by way of derogation from Article 9 of the GDPR (general prohibition of processing such categories of personal data): depending on the specific circumstances of a clinical trial, the applicable legal bases pursuant to art. 9 of the GDPR could be both "reasons of public interest in the public health sector" pursuant to art. 9.2 lett. i) both "scientific research" pursuant to art. 9.2 lett. j).

4.7 Data Subjects' Rights

MUW, UPG, KI, THL, FHJ, and COMB are responsible for ensuring that the applicable rights of the data subjects can be exercised, under the provisions of the GDPR, depending on the legal basis for personal data processing. The exercise of rights is free of charge.

Rights when the processing is based on the controller's legitimate interest:

- Right to obtain information on the processing of personal data
- Right of access
- Right to rectification
- Right to erasure (right to be forgotten)
- Right to restriction of processing
- Right to object
- Notification obligation regarding rectification or erasure of personal data or restriction of processing

4.7.1 Right to obtain information on the processing of personal data

Data subjects have the right to be informed of the collection and processing of their personal data. The processing of personal data shall be done transparently.

Data subjects have to be informed about:

- the name and the contact information of the controller;
- the purposes for which the data is being processed;
- the legal basis for the data processing;
- the processing times of the data;
- to whom the data is disclosed;
- the disclosing of data outside the EU or EEA;
- the rights as a participant; the source of the data if it is not obtained directly from the data subject.

4.7.2 Right of access

Data subjects have the right to receive confirmation from the controller on the processing of personal data that concerns them. The data subjects thus have the opportunity to evaluate and ensure the legality of the processing.

If data concerning the data subject is being processed, the controller must provide the data subject with a copy of the personal data being processed. If the data subject makes the request, this is known as a "Data Subject Access Request (DSAR)".

If the subject wishes to make a DSAR, he can proceed by filling out the appropriate form **(ANNEX 6)** and following the instructions contained therein to return to the PI of the clinical center and the local data protection officer's contact details.

4.7.3 Right to rectification

Data subjects have the right to demand the rectification of inaccurate personal data concerning them and to have incomplete personal data completed.

The data controller must respond to the data subject without undue delay and no later than one month from receipt of the request. In the reply, the owner indicates the measures that he/she has adopted following the request. If the requests are numerous or complex, the owner can reply that he needs more time to process them. In these cases, the deadline can be extended by up to two months. Justifications must be provided for the extension. When an interested party requests data rectification, the data controller must assess whether the data in question is incomplete or inaccurate for the purposes of the processing.

If the data controller believes that, despite the opinions of the data subject, the data are not inaccurate for the purposes of the processing, he is not required to rectify them. In such cases, the data controller must respond to the data subject within one month with a justified reason not to correct the data. After that, the data subject can refer the matter to the data protection officer if he wishes.

4.7.4 Right to erasure (right to be forgotten)

In some instances, the data subject has the right to have the controller erase data concerning him or her without undue delay. This right is also known as the right to be forgotten.

This right does not apply if the processing of the data is necessary:

- for reasons of public interest in the area of public health;
- for scientific or historical research purposes or statistical purposes in so far as the right to erasure is likely to render impossible or seriously impair the achievement of the objectives of that processing.

4.7.5 Right to restriction of processing

The data subject can request the controller to restrict the processing of personal data concerning him or her. Art. 18 of the GDPR establishes the right of the interested party to have his data used limited to what is necessary for the purpose of conservation.

The data can be processed only for the purpose of their conservation unless there is the consent of the interested party or if such processing is necessary for "the exercise or defence of a right in the judicial or to protect the rights of another natural or legal person or for reasons of significant public interest of the European Union or of a Member State "(Art. 18 par 2 GDPR).

4.7.6 Right to object

In certain situations, the data subject has the right to object to processing his or her personal data, that is, request the controller not to process it at all.

Suppose the data is processed for the performance of a task carried out for reasons of public interest, in the exercise of official authority, or for the purposes of the compelling legitimate interests pursued by the controller or a third party. In that case, the data subject has the right to object to the processing on grounds relating to his or her particular situation. In such cases, the processing must be stopped.

If the personal data is processed for scientific or historical research purposes or statistical purposes, the data subject may object to the processing on grounds relating to his or her particular situation, in which case the processing must be stopped. The right to object does not apply, however, if the processing is necessary for the performance of a task carried out for reasons of public interest.

4.7.7 Notification obligation regarding rectification or erasure of personal data or restriction of processing

The controller shall communicate any rectification or erasure of personal data or restriction of processing carried out following Article 16, Article 17(1), and Article 18 to each recipient to whom the personal data have been disclosed, unless this proves impossible or involves disproportionate effort. The controller shall inform the data subject about those recipients if the data subject requests it.

4.8 Storage of the personal data

All the data that is going to be collected from different sources (including data collected from the LETHE app, the external cTRAIN/cCog app, the mobile phone, the smartwatch, and the professional dashboard) is going to be stored at the secure cloud-based server by EGI Foundation (EGI - Science Park 140, 1098 XG Amsterdam,

Netherlands) in the LETHE backend. To ensure that these data sources are merged correctly, they are all connected with the participant's Lethe dummy Google account. To maintain participant confidentiality, these dummy accounts that do not contain any identifying data are going to be used for that purpose. A document linking dummy accounts and identification numbers to individuals will be kept strictly confidential by the investigator at the clinical center.

The PI will be responsible for storing and archiving all trial documents at each site. All trial documentation, including that held at participating sites and the LETHE backend, will be stored for 15 years following the end of the study at the clinical institutes (MUW, UPG, KI, THL):

- Medizinische Universität Wien (MUW), Spitalgasse 23, A-1090 Vienna, Austria
- Universita degli Studi di Perugia (UPG), Piazza dell'Università 1, IT-06123 Perugia, Italy
- Karolinska Institutet (KI), Department of Neurobiology, Care Science and Society (org. no. 202100-2973), Department Management, level 3, section D Alfred Nobels Allé 23, 23400, SE-141 83 Huddinge, Sweden
- Finnish Institute for Health and Welfare (THL), Mannerheimintie 166, FI-00271 Helsinki, Finland

Data of the screening visit will only be stored at the clinical center, where the screening takes place. For participants that are included in the study, this data will be added to the LETHE backend.

The individual participant data collected with the LETHE app (including self-reported data, e.g., questionnaires and automatically recorded data e.g., log-ins and other engagement with the components of the app) will be stored in a cloud-based system provided by EGI.

Data collected by the cognitive training (cTRAIN) and testing app (cCOG) is primarly stored at Microsoft Azure servers located in the Netherlands. Data that are of interest for this study will be transferred to the LETHE backend.

Participants will be required to accept the terms and conditions of any external/third-party applications and services used in the study. External/third party means applications or services that are not designed by the consortium or individual project partners but are required for the implementation of the study. These include Google and Fitbit, which are necessary to enroll in the trial, and YouTube and WhatsApp, which are needed for the intervention program. Regarding WhatsApp, the only data collected during the project is whether the participant has joined or not. The content of the chats is neither stored in the LETHE system nor analyzed during this project.

Data collected and generated by these devices/applications will be stored and handled by the respective companies as stated in their terms and conditions and privacy policy documents. Data collected with the LETHE app (self-reported or automatically collected) or any participant data collected during the study visits will not be shared with the external service providers. Data collected by the external applications or devices will also be stored in EGI cloud service, combined, and handled together with all other participant data collected in the study at the LETHE backend.

In addition to that, also data (pseudonymized) sources are transferred to other project partners in order to store and analyze them (like blood samples or MRI scans) for future investigations: blood-based on dementia-related biological research; MRI data, together with basic demographic data, can be used to generate

normative/reference data for novel tools that are used to identify characteristics of cognitive disorders and evaluate their treatment.

- MRI, cTRAIN, and cCOG data will also be stored at Combinostics own server on the Microsoft Azure platform. Combinostics uses the “West Europe” data center located in the Netherlands.
- Blood samples will be stored at the “Medical University of Vienna” (MUW, Spitalgasse 23, A-1090 Vienna)

5 LETHE Informed consent Form (ICF)

A common general informed consent in English has been developed as Annex 1 to D10.1 like a template for developing a specific Lethe Informed Consent Form (ICF). For this adapting process, we are started by updating ad extending the informed consent form and privacy sheets attached to D10.1.

The Lethe consensus was developed together to achieve a standard model for all four countries. The key details of the protocol and privacy policy have been defined to be necessarily included in the native language versions of each country and described in a similar way. However, each country will have flexibility when translating consent forms to modify and adapt them as needed based on legal requirements and local practices.

According to the Study Protocol (Version 1.1/22.06.2022) we don't use the original full name of the study, *"A personalized prediction and intervention model for early detection and reduction of risk factors causing dementia, based on AI and distributed Machine Learning"* in the ICF modules and the pilot trial. We need a shorter and simpler name, but above all, more understandable for the participants. For this it was agreed between LETHE partners to use the name: *"Digitally supported lifestyle program to promote brain health among older adults- the LETHE pilot trial. A 24-month, randomized controlled, parallel-group, multicentre pilot trial in Austria, Finland, Italy, and Sweden".*

5.1 Obtaining consent

As written in the study protocol (Version 1.1/22.06.2022) and according to D10.1, prior to study enrolment, written informed consent must be obtained from each participant. Written informed consent will be obtained after an adequate explanation of the aims, methods, source of funding, the anticipated benefits and potential risks of the study, and the discomfort it may entail. The person obtaining consent must be satisfied that the participant has understood the purpose and the nature of the study and what the study involves. Written informed consent will be obtained for the screening procedure (at the screening visit) and another one for randomization and trial participation (at the baseline visit). If the screening visit is conducted remotely, the consent for the screening can also be provided verbally at the beginning of the assessment if needed. The participant will be asked to sign and return a written consent form by post afterward. All participants are capable of consenting themselves (see exclusion criteria in the study protocol - Version 1.1/22.06.2022).

It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care and with no obligation to give a reason for withdrawal. The person who decides to withdraw his consent to participate in the trial does not automatically withdraw his consent also to the processing of his personal data. The person who chooses to withdraw his consent to participate in the trial does not automatically withdraw his/her consent to the processing of his personal data as well. Therefore, a form has been developed that the person can use to withdraw his/her consent to the processing of his/her personal data. The following document will be available in annexes to support the privacy monitoring activities:

• **Data Subject Consent Withdrawal Form - ANNEX 7**- a document used by the data subjects to withdraw their consent.

Potential participants will be given enough time to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of the participant's dated signature and the dated signature of the person who presented and obtained the Informed Consent. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site.

Individual consent will be collected from the study partner if they are asked to provide any additional information about the participant during the study (e.g., CDR assessment either in person or by phone/remotely). This consent can also be verbal (a signed form can be sent afterward). The study partner can be, e.g., a friend or family member who may or may not live with the participant. Having a study partner is preferred but not mandatory. As the target population is at-risk individuals without dementia or substantial impairment, the primary role of the study partner will be as an informant.

Each country will translate and implement adaptations to meet both EU and national legal and ethical requirements. Each country will submit to the local Ethical Committee the version of the ICF in its language and which reports the specific laws for the country.

5.2 Screening procedure

The Lethe consortium has decided to produce an informed consent form and privacy sheet for the screening visit. This form is complete and compliant with the standards mentioned above and only describes the study procedures included in the screening visit:

The screening visit will be organized for those invited people who express their interest in the study. The screening phase comprises 4 steps which can be executed during one visit or several separate visits on different days depending on the local arrangements (as long as their order is maintained as described below). The four sequential screening visit steps are as follows:

- Introduction, answers to any questions, providing the consent for screening before the participant undergoes any procedures (step 1 carried out by the study nurse or physician, based on local regulation)
- Evaluation of inclusion criteria, assessment of CAIDE risk score, and cognitive performance (MMSE and CERAD word list learning) (step 2 carried out by the study nurse, psychologist, or physician)
- If eligible based on step 2 (inclusion criteria), evaluation of the presence of exclusion criteria (step 3 carried out by the study physician)
- Discussion of the participant’s assessment results and reasons for inclusion/exclusion for all individuals regardless of the screening outcome.

Participants meeting the eligibility criteria will receive the participant information sheet and Informed Consent Form for the 24-month trial, and arrangements will be made for the baseline visit.

Only the participants deemed eligible for the trial based on inclusion criteria (step 2) will be invited to the medical examination (step 3). Therefore, the cognitive assessment for eligibility must always precede the medical examination. However, all participants will receive information on the reason for the inclusion in/exclusion from the trial (step 4). To account for potential movement restrictions (e.g., due to the COVID-19 pandemic) or depending on participant availability, the screening can take place on-site or remotely via

video conference. Depending on local procedures, the consent for screening can also be provided verbally if the visit takes place remotely.

Researchers and other study staff members are committed to following Good Clinical Practice (GPC) and research ethical guidelines.

Each participant will be provided with an ID code-named “screening code” when he/she accepts to join a screening procedure. The data protected by this code is called Pseudo-anonymized.

The name and contact details of the screening participants will never be made public; only members of the study staff at each clinical center who have signed a confidentiality agreement know the identity. The code that enables this pseudo-anonymized data to be assigned to the subjects are only kept at the study center that performed the screening procedures. The list containing the names and contact information of the participants in the screening and the "Screening ID" will be kept separately at the clinical centers to ensure the pseudo anonymization of the data under the privacy regulations. All the material used for the screening procedure will be stored in each site until the end of the project in a safe place with limited access only to authorized persons; after these, the site will proceed to archive in totally anonymization form or destruction according to the regulations in force.

The data of the people eligible for the study and agree to participate will be added to the professional dashboard to the LETHE backend after signing the main ICF and Privacy sheet form. This decision was made to streamline procurement and allow clinical centers to extend screening to as many people as possible and implement the recruitment phase of the study, maximizing the chances of reaching the target number of people to be included in the established time.

A register will be produced at each clinical center to keep track of the subjects who were eligible for the study by screening and agreeing to participate. This file reports The Screening ID, the Screening failure, the Lethe ID subject assigned by randomization, the date of enrolment in the study and the signature of the investigator **(ANNEX 8)**.

5.2.1 ICF for screening

“You are being invited to participate in a screening assessment for Study “Lethe” which aims to investigate the feasibility of a digitally delivered lifestyle program to support brain health in older adults.

Screening means that the study staff will assess based on your health status and characteristics whether you are eligible to participate in this Study. Before any of the assessment you will be required to read and sign this consent document. If the study site staff considers you to be eligible based on the screening assessment you will be received additional more detailed information about the main study and you will be asked to sign a separate informed consent. This information sheet describes the screening assessment and what you are asked to do. It also contains a brief description of the main study.

After reading this information form carefully, please take your time to decide if you are interested in participating. Before deciding, you can discuss your participation with friends and family and with health professionals. If you have any questions, please contact the study staff (contact details at the end of the document).

You can refuse to participate, or you can change your mind and withdraw your consent at any time for any reason, without giving any justification, without penalty or loss of benefits to which you would still be entitled and with no effect on your future or current medical care. In case you decide to withdraw the consent, please contact the study staff. If you withdraw your consent, your data collected up to that point can be used as part of the research.

BACKGROUND AND AIM OF THE STUDY

Research has shown that a healthy lifestyle, including a balanced diet, physical and social activity, and management of vascular risk factors (e.g., blood pressure, cholesterol) can support both cardiovascular and brain health. In a landmark Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), a multimodal lifestyle program had clear benefits on older adults' memory, functioning, and quality of life. More research is needed on whether and how such a lifestyle program could be delivered with the help of new digital tools, such as smartphone and mobile applications.

The main objective of this clinical study is to assess the feasibility of an ICT-assisted lifestyle interventional approach in older adults, in order to support active and healthy ageing. We will assess how well participants adhere to the lifestyle program and the digital solutions offered to them. We will also assess how participants' lifestyle (e.g., diet and physical activity) and other risk factors relevant for cognitive decline and dementia (using validated risk scores) change over time. Other objectives in the LETHE project include investigating and identifying risk and protective factors and mechanisms related to healthy aging, brain health, and cognitive decline, using also machine learning based approaches and prediction modelling.

The LETHE pilot trial will be conducted at four European study sites (Medical University of Vienna in Austria, Finnish Institute of Health and Welfare in Finland, University of Perugia in Italy, and Karolinska Institute in Sweden). A total of approximately 160 participants will be recruited. In Finland/Sweden/Italy/Austria, we will recruit approximately 40 persons. We will invite older people aged 60-77 who do not have any substantial cognitive impairment but have some risk factors for cognitive decline. These include education level, systolic blood pressure, total cholesterol, body mass index, and level of physical activity. Participants should also be able and willing to use an Android smartphone to follow lifestyle program given in the trial and to fill in questionnaires.

After screening, eligible individuals will be randomly divided into 2 equally sized groups, the self-guided and structured lifestyle groups. In brief, both groups receive evidence-based lifestyle advice and guidance, but the content, delivery, and intensity will be different for the different groups. Both groups will use digital tools (smartphone, wrist-worn smartwatch) for the entire duration of the study (24 months), but these tools will be used differently in the different groups. The lifestyle program will cover diet, physical activity, social activity, mental stimulation, stress, sleep, and management of vascular risk factors (elevated blood pressure, blood glucose and lipids, smoking, overweight, monitoring of cardiovascular disease such as diabetes). Participants in the self-guided group will be given health and lifestyle-related advice and recommendations which they can implement independently. Participants in the structured group will receive more intensive and tailored guidance based on their personal characteristics, and they will be invited to attend scheduled sessions.

SCREENING PROCEDURE

The screening phase comprises 4 steps which can be executed during one visit or several separate visits on different days depending on the local arrangements. Screening visit will last for max. 2,5 hours. Screening visit can take place either at the study center or remotely (via video call, if the center uses this method).

The four sequential screening visit steps are as follows:

1. Introduction, answers to any questions, signing the consent for screening

2. Evaluation of inclusion criteria, assessment of cardiovascular risk factors and other risk factors relevant for dementia; two short tests of cognitive performance. If the screening takes place at the study center, your height, weight, blood pressure, pulse, and hip and waist circumference will also be measured.

3. If eligible based on step 2 (inclusion criteria), study physician will assess your current health and medical history to confirm the eligibility.

4. Discussion of the participant's assessment results, reasons for inclusion/exclusion, for all individuals regardless of the screening outcome.

POTENTIAL BENEFITS AND RISKS OF THE STUDY

The screening assessments may help detect certain health problems and enable early intervention. You will be informed about any information potentially relevant for your health. Through your participation in this study, you can advance aging- and dementia-related medical research.

Screening assessments are not expected to cause any harm and they do not involve any risks. Some persons may feel tired or experience frustration when completing the memory and cognition tests. You can always interrupt the test or refuse to answer to questions you feel uncomfortable with.

You will not be charged any costs for materials, visits, or any study-related procedure performed during this screening visit or during the study. You will not receive any compensation or reimbursement for your participation.

STUDY PARTNERS AND FUNDING

This study follows European data protection regulation. Researchers and other members of the study staff are committed to follow good clinical practice and research ethical guidelines.

The study is conducted by <Clinical Partner name>. The Principal Investigator is < Name of clinical center PI>. The Principal Investigator in <Country> with responsibility for the safety of <country> participants is <Name>.

Medizinische Universität Wien (MUW), Universita degli Studi di Perugia (UPG), Karolinska Institutet (KI), Finnish Institute for Health and Welfare (THL), FH JOANNEUM and Combinostics Oy (COMB) as "data Controller" are responsible for the lawfulness of the processing of personal data in the context of the study.

Extra Red Srl (ER), Infotrend Innovations Company Limited (INFO), Idryma Technologias Kai Erevnas (FORTH) and EGI Foundation (EGI) as "processors" play a role in the processing of your data and have accepted a data processing agreement aimed at ensuring that personal data is not processed illegally, wrongfully or processed in way that results in unauthorized access, alteration, erasure, damage, loss or unavailability.

IPHC / SCIGNE platform. Fitbit (FB), Kaasa Solution GmbH (KA) and Google are defined as "sub-processors" and are hired by processors to carry out specific Processing activities on behalf of the Data Controllers.

Study is funded by the European Union's Horizon 2020 research and innovation programme under grant agreement no 101017405.

SHORT DESCRIPTION OF PROCESSING OF PERSONAL DATA AND PRIVACY INFORMATION

In this clinical study, the study physician and the site staff will collect and record data relating to you only if this is essential for the conduct the study as described to you or for achieve its objectives.

The information collected by this research project will be kept confidential, except for disclosure under the law or as described in this informed consent form.

You will be provided with an ID code named "screening ID" when you enter the study. Data related to the study will only refer to you using this subject code. The data protected by this code is called Pseudo-anonymized.

Your name and contact details will never be made public, only members of the study staff who have signed a confidentiality agreement know your identity.

Only the following people will be able to connect to the Your identity to your subject code at the study center:

The study doctor and the people with whom he collaborates at the experimental center for the purpose of conducting the study.

Authorized representatives of the study site who are bound to secrecy, as well as representatives of national and/or foreign health authorities and the relevant ethics committees, may inspect this data insofar as this is necessary or prescribed for checking the proper conduct of the clinical study.

For this reason, it will not be possible to guarantee absolute secrecy. In the unlikely event that security is compromised and your personal data becomes available properties, we will notify you, the data protection authority and another partner jointly responsible for the lawfulness of the protection of your personal data.

What data do we collect about you?

By signing this Information Sheet and Informed Consent Form, you acknowledge that the study physician and his staff must collect and use your personal data if you wish to participate in the screening procedure. Without these data we can't check if you are eligible for the study.

The data we will collect includes all the areas listed in the "screening procedure" section of this document.

All persons who have access to this data are subject to the applicable national data protection regulations and/or the EU General Data Protection Regulation (GDPR) when handling the data. The code that enables this pseudo-anonymized data to be assigned to you is only kept at your study center.

How will we protect your data?

In the context of this clinical study only named persons in the research group can process your personal data (persons for whom it is necessary in order to carry out their job tasks).

How long will your data be stored?

The paper documents of screening procedure will be conserved at this clinical center, according to law, until the end of the project, after these, the site will proceed to archiving in anonymization form or destruction according to the regulations in force.

if you are eligible for the study, you will be invited to participate in the full trial and if you decide to join more personal data are collected from additional sources and you will be asked to use different digital tools (such as mobile phone, apps, google account and more). Information sheet for the full trial will contain all additional information about this aspect and describe in detail haw this data are processed and stored.

Also, if you will be invited to participate in the full trial and you decide to join, the data collected from all you in the screening visits will be saved and storage together with all other data collected in the full trial in pseudo-anonymized form on a server (EGI Foundation) outside the clinical center till the end of the study period; After the LETHE study period all trial data will be stored at the clinical centers (KI, MUW, THL, UPG) for 15 years. All persons who have access to this data are subject to the applicable national data protection regulations and/or the EU General Data Protection Regulation (GDPR) when handling the data.

Pseudonymized research data may also be shared with international collaborators and partners outside the LETHE research group (not all of whom are known yet), for research purposes outlined in the research plan. In this situation, some of the pseudonymized data may be transferred outside EU/EEA to countries where the level of data protection may be lower. LETHE research group will in this case ensure that appropriate and safe measures will be followed when transferring and processing the data and all partners are committed to handle the data confidentially.

Only the pseudonymized or anonymized data will be used for any publication of the study results.

If you have any questions about this screening procedure or this research study, or in case of any problems, doubts or complaints contact your site staff at the telephone numbers listed below.

• XXXXXXXXXX

What are the legal bases for processing your personal data?

Processing necessary for the pursuit of the legitimate interest of the data controller (Article 6, paragraph 1, letter f), in conjunction with Article 9, paragraph 2, letter i) or j), GDPR).

What are the rights of the participants?

You can revoke your consent to the collection and processing of your data at any time without justification. If you withdraw your consent to participate in this study, your personal data and study data about you collected prior to such withdrawal may continue to be used as described above. Once you have withdrawn your consent to participate in the study, no further data will be collected on your account for the purposes of this study, unless you decide otherwise, for example, you agree to undergo further tests. If you consent to the collection of additional data after withdrawing your consent, such study data may also be used as described above.

Please note that you have the right to be informed about the processing of your personal data and to request that the processing of your personal data be restricted. You also have the right to review your information and request that it be corrected or supplemented if, for example, you find an error in it or it is incomplete or inaccurate. You also have the right to object to the processing of your personal data.

However, in the context of scientific research, these rights may be restricted. The law may oblige the data controller to retain your research data for a certain period of time, regardless of the data subject's rights. The law allows exceptions to the data subject's rights when it is necessary to ensure the results of scientific research and the safety of the subjects. You have the right to receive the information free of charge and within a reasonable time (within one month of the request). If your request for information is very large or for any other justified reason the collection of information takes a long time, the deadline can be extended by a maximum of two (2) months. You will be informed of the extension and the reason for it.

If you wish to exercise these rights or make a complaint, please contact your practice doctor or data protection officer (a staff member at your practice center who is responsible for verifying that personal data is kept confidential).

- XXXXXXXXXXXXXXXXXXXXX
- The data protection officer for personal data at clinical site is XXX (e-mail address of DPO: xxx)
- contact of national GUARANTOR OF PRIVACY

CERTIFICATE OF CONSENT

Please see the **ANNEX 9** to this document

5.3 Main consent form for the subject and privacy sheet

You are being asked to participate in a study which aims to investigate the feasibility of a digitally delivered lifestyle program to support brain health in older adults.

We invite you to enrol because you have attended the screening visit and based on those assessments you meet the eligibility criteria for the trial.

Before deciding whether or not you wish to participate in this study, it is important that you understand why this research is being done and what you are asked to do if you agree to participate in the study.

• Part I - Information form: explains why this study is being conducted and what will happen if you participate. Describes also your right to withdraw from the study at any time.

• Part II - Certificate of Consent: If you agree to participate, the doctor/practice staff will ask you to sign and date this consent form.

After reading the information form carefully, please take your time to decide if you are interested in participating. Before deciding, you can discuss your participation with friends and family and with health professionals. If you have any questions, please ask your doctor/study staff to provide you with further information (contact details at the end of the document).

Part I: INFORMATION FORM

1. GENERAL INFORMATION AND PURPOSE OF THE STUDY

Research has shown that a healthy lifestyle, including a balanced diet, physical and social activity, and management of vascular risk factors (e.g., blood pressure, cholesterol) can support both cardiovascular and brain health. In a landmark Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), a multimodal lifestyle program had clear benefits on older adults' memory, functioning, and quality of life. More research is needed on whether and how such a lifestyle program could be delivered with the help of new digital tools, such as smartphone and mobile applications.
The main objective of this clinical study is to assess the feasibility of a digitally delivered lifestyle program to support active and healthy ageing in older adults. We will assess how well participants adhere to the lifestyle program and the digital solutions offered to them. We will also assess how participants' lifestyle (e.g., diet and physical activity) and their risk of developing dementia based on validated risk scores change over time. Other objectives in the LETHE project include investigating and identifying risk and protective factors and mechanisms related to healthy aging, brain health, and cognitive decline, using also machine learning based approaches.

2. SELECTION OF PARTICIPANTS

The LETHE study will be conducted at four European study sites (Medical University of Vienna in Austria, Finnish Institute of Health and Welfare in Finland, University of Perugia in Italy, and Karolinska Institute in Sweden). A total of approximately 160 participants will be recruited. In Finland/Sweden/Italy/Austria, we will recruit approximately 40 persons. We will invite older adults aged 60-77 who do not have any substantial cognitive impairment but have some risk factors for cognitive decline. These include education level, systolic blood pressure, total cholesterol, body mass index, and level of physical activity. Participants should also be able and willing to use an Android smartphone to follow lifestyle program given in the trial and to fill in questionnaires.

3. VOLUNTARY PARTICIPATION

It is up to you to decide whether to participate in the study. Your doctor/site staff will describe it to you and review this information with you, and a copy of this form will be provided to you to take home. Before deciding, you can talk about your participation with friends and family and with your personal (family) doctor. You can refuse to participate, or you can change your mind and stop participating and withdraw your consent at any time for any reason, without giving any justification, without penalty or loss of benefits to which you would still be entitled and with no effect on your future or current medical care. In case you decide to withdraw from to study please see the relevant section of this document.

4. RIGHT TO REFUSE OR WITHDRAW

You are not obliged to participate in this study if you do not wish to do so. You can also interrupt participation in the research at any time without explaining. If you want to stop participating, we will use all data collected up to the time you stop the participation. It is your choice, and all your rights will be respected. There will be no penalties either loss of benefits to which you would otherwise be entitled, and there will be no effect on your medical treatment future. This decision will not affect the standards of care you receive. If you leave the study for any reason, your doctor / study staff may ask you to undergo some end-of-study tests to verify the effect that the intervention had until your withdrawal.
However, it is also possible that the study physician decides to prematurely terminate his participation in the clinical trial without having obtained his prior consent. The reasons for this can be:
(a) you cannot meet the requirements of the study;
(b) The study physician has the impression that further participation is not in his interest.

5. STUDY PROCEDURES

The duration of the study is 24 months for each participant. The interventions in this clinical trial are expected to run for 24 months, however, individual examinations will be carried out up to 1 month after the end of the study (in the 25th month after the start of the study). At the beginning of the study (baseline visit) at the study center, participants will be randomly divided into two equally sized groups (to determine which type of a lifestyle program they will follow during the study period, a structured or self-guided program). Both groups will receive evidence-based lifestyle advice and guidance according to the same principles, but the content, delivery, and intensity of the guidance will be different for the different groups. You do not get to choose the group yourself, and study staff will not actively disclose the group assignment during the study.

- **Self-guided intervention:** participants will be given health and lifestyle-related advice and recommendations which they can utilize and implement independently.
- **Structured intervention:** the guidance will be more intensive and tailored, and participants will be invited to attend different scheduled sessions individually and in small groups, both face to face and remotely. Study staff can also contact participants in the structured intervention group by email/phone.

Regardless of which group you belong to, you will be asked to use specific digital tools for the entire duration of the study (24 months). These include an Android smartphone (new study phone or participant's own phone if compatible), a tablet (will be provided if needed for the participants of the structured intervention group) and a wrist-worn smartwatch (Fitbit). All devices have CE certification and are used only for their intended purpose. You will be asked to use an application on the smartphone which has been specifically designed for this study (the LETHE app), for this reason it is necessary that you have an Internet connection. The app contains information about healthy lifestyle and different questionnaires for you to fill in during the study. The LETHE app sends the subject's data directly to the LETHE backend, without sharing it with any 3rd party. The exact content of the app and activities you will be asked to complete depend on which group you belong to (structured vs. self-guided). You will receive separate detailed instructions on how to use the digital devices. A Google account is required to use the app. In order to protect your identity, dummy accounts, not containing any identifying data, are created and used for the set-up of the mobile phone and the Fitbit smartwatch.
Regardless of which group you belong to (structured or self-guided), you will be invited to attend four main study visits at the study center: **baseline** (at beginning of the study), at **months 6~~,~~** at **month 12** and at **months 24** (end of the study). Each visit will last approximately 4-5 hours and assessments can be completed during one day or split over several days; only the visit month 6 will be shorter (approximately 1 hour).

Procedure	baseline visit	visit Month 6	visit Month 12	Visit month 24
Informed consent and Privacy form	x			
Subject characteristics (basic personal information, contact details, education and marital status, family history of cognitive disorders	x			x
medical history and medication use	x	x	x	x

measurements (BMI, Blood pressure, hip-waist circumference)	x	x	x	x
Blood sample	x	x	x	x
DNA blood test (APOE)	x			
Brain magnetic resonance imaging	x			x
Tests of cognitive performance and functional status	x		x	x
Physical performance (e.g., balance and walking test)	x			x

Regardless of which group you belong to (structured vs. self-guided), you will also be asked to fill in questionnaires independently in the LETHE app. Most of these questionnaires will be completed 3 times during the study, close to the date when you come to the study center for other assessments (baseline, month 12, month 24). You can complete the questionnaires at a time and place suitable for you. Questionnaires are related to your lifestyle habits (e.g., diet, physical activity), mood, sleep, symptoms of stress, and attitudes towards new technologies and health-related topics. In addition, the LETHE app will store other data that you can enter yourself (e.g., blood pressure) and data that is automatically registered passively, such as how often or how long you visit and use the app, the contents of messages or calls are not stored in any way. We will also ask you to complete a digital memory and cognition test battery 3 times during the study, approximately 1 month after each main study visit. You can use your own computer or tablet and complete the test at a time and place suitable for you. Alternatively, you can come to the study center to complete the test.

The Fitbit smartwatch which you receive at the beginning of the study is supposed to be worn continuously during night and day. The watch records automatically data (e.g., on your physical activity level and other parameters such as heart rate, heart rate variability, and sleep parameters) through motion sensors.

In addition, data is continuously collected via your mobile phone, specifically the number of active Bluetooth device in your mobile phone, and time of the app use.

It may happen that you will be offered to use other apps and service during the course of the study (e.g., google calendar, WhatsApp, YouTube). If this is the case, LETHE will only record when and how often this app is accessed via LETHE app. An exception to this is the app for cognitive training, in which case your tests are also stored.

We will ask you to name a family member, relative, friend or other person who knows you well and could provide some information about you and your health during the study (if you decide to participate). We will not disclose any information about you or your assessments / test results without your permission. You can participate even if you cannot/want to name any person.

It is not possible to give guarantees or assurances relating to study results. It is possible that you will not benefit directly from participating in this study. However, you will be informed about the results of your health examinations and other potentially relevant aspects concerning your health. You will also receive information about health lifestyle and practical advice and guidance. Through your participation in this study, you can advance aging- and dementia-related medical research.

Participant in this trial does not involve taking any new medication, if deemed necessary based on test result, participants will be advised to consult to a GP or specialist who will assess t if treatment is needed.

6. BIOLOGICAL RESEARCH

Blood samples will be collected both for routine assessments, such as e.g., cholesterol and blood glucose levels, and for research purposes related to this study. Blood samples will be collected for the determination of genotype and other genetic factors, and some blood will also be fast frozen and stored for future investigations on dementia-related blood-based biomarker studies. One serum tube will be sent to the Medical University of Vienna to measure potential serum biomarkers related to dementia. These analyses can be performed by a project partner or future project partner. Neither you nor the doctor / study staff will receive the results of this tests as the results will not affect the medical treatment you will receive.

(Only for the MUW - UPG- clinical center) Storage of blood samples for future research are optional. In order to participate in the study, you are not obliged to agree to keep your blood samples for research or to undergo testing future. If you accept, you will be asked to sign and date a separate consent form.

7. BRAIN IMAGING

All of the study participants will also be invited to perform a brain magnetic resonance imaging- MRI scan. This is a common procedure to collect information about the structure of the brain. MRI can also provide information about potential abnormalities such as stroke and tumors. The scan will be conducted twice during the study (at baseline and at month 24). Scans will be organized separately outside the other study visits, and one scan lasts about 30 min. You will receive the results of this examination.

8. RISKS ASSOCIATED WITH THE STUDY PROCEDURES

Following the lifestyle program (structured or self-guided) and participating in this study is not expected to cause any harm and does not involve any major risks. We will ask regularly about any adverse effects you experience and intervene immediately if needed. Possible common inconveniences that may occur are the following:

- Participation can be time-consuming (study duration for each participant 24 months)
- Some persons may feel tired or experience frustration when completing for example cognitive tests or other questionnaires, or when engaging with the digital devices. You are free to decide which questions you want to answer, and how often to engage with the mobile app and for which purposes. You will receive instructions on how to use the devices, and we will assist you in case there are any technical problems.
- If you frequently used a Google service (e.g., google account) the use of new google Lethe dummy account may be uncomfortable at first, however, you can use them at the same time.
- During physical performance tests there is a risk of losing balance or falling. We will minimize this risk by standing on your side and help you, if needed.
- Exercise training may cause some muscle soreness and stiffness. This is temporary and usually lasts only up to a few days. You will receive instructions on how to exercise safely to avoid any injuries.

8.1 RISKS ASSOCIATED WITH THE STUDY'S MEDICAL PROCEDURES

- Risks associated with taking blood samples: Blood will be drawn from a vein arm using a syringe and needle. This could cause some discomfort or bruising bleeding at the puncture site. There is also a minimal chance of infection. Other risks, although rare, include dizziness and fainting.
- Risk associated with MRI scan if you decide to undergo this exam: MRI does not cause any pain or discomfort, and there is no radiation dose. One scan lasts about 30 min and you should lay still during this time. The main discomfort may be claustrophobia (fear of being trapped in a tight place). The machine produces loud noises and a pounding sound; however, these noises can be muffled by using protective headphones. Headphones allow you also to communicate with the staff during the scan. There are no known harmful side effects related to short exposure to the strong field magnetic used by MRI scanners. The greatest risk is represented by the presence of metal objects inside or outside your body. Before your participation in the study, you will be asked about any metal implants or potential metal fragments present in the body that may create a health risk or interfere with imaging tests.

9. STUDY PROCEDURES IN THE CONTEXT OF THE COVID-19 PANDEMIC

The interventions have been planned to be partly deliverable in a remote setting. Still, some of the study procedures (e.g., blood sample collection, physical measurements and cognitive outcomes assessment) will require an on-site physical visit. In these cases, visits that may not be conducted in person at the study site at the scheduled time (due e.g., COVID-19 related restrictions or other travelling difficulties) will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits are possible.

10. INSURANCE AND COSTS FOR PARTICIPANTS

Participants are insured as follows *<XXX (Each clinical center will specify the procedure here)>*.

You will not be charged any costs for materials, visits, or any study-related procedure performed during this study. You will not receive any compensation for participating in this study.

11. SHARING OF RESULTS

The results of this study could be published in a medical journal or technology and presented in scientific congresses. You will not be identified (with your name or any other way) in any of these publications.

A description of this clinical trial will be available on the website “www.lethe-project.eu”. The website will not contain information that can identify you. At most, the website will present a summary of the results. You can consult the website at any time. This website may only be available in English; if you need assistance, talk to your doctor at study site.

12. STUDY PARTNERS AND FUNDING

The study is conducted by *<Clinical Partner name>.* The Principal Investigator is *< Name of clinical center PI>.* The Principal Investigator in *<Country>* with responsibility for the safety of *xxx* participants is *<Name>.*

Medizinische Universität Wien (MUW), Universita degli Studi di Perugia (UPG), Karolinska Institutet (KI), Finnish Institute for Health and Welfare (THL), FH JOANNEUM and Combinostics Oy (COMB) as “data Controller” are responsible for the lawfulness of the processing of personal data in the context of the study. Extra Red Srl (ER), Infotrend Innovations Company Limited (INFO), Idryma Technologias Kai Erevnas (FORTH) and EGI Foundation (EGI) as “processors” play a role in the processing of your data and have accepted a data

processing agreement aimed at ensuring that personal data is not processed illegally, wrungfully or processed in way that results in unauthorized access, alteration, erasure, damage, loss or unavailability.
IPHC / SCIGNE platform. Fitbit (FB), Kaasa Solution GmbH (KA) and Google are defined as "sub-processors" and are hired by processors to carry out specific Processing activities on behalf of the Data Controllers.

Study is funded by the European Union's Horizon 2020 research and innovation programme under grant agreement no 101017405.

13. FURTHER INFORMATION AND CONTACTS

If you have any questions about this research or this research study, or in case of any problems, doubts, complaints, you can contact your doctor's office at the telephone numbers listed below.
. <Add contact details>

14. SHORT DESCRIPTION OF PROCESSING OF PERSONAL DATA AND ITS CONFIDENTIALITY

Contact details of the data protection officers of the institutions mentioned:

- Data Protection Officer of the Medical University Vienna (MUW): datenschutz@meduniwien.ac.at
- Data Protection Officer of the University of Perugia (Italy): rdp@unipg.it
- Data Protection Officer at Karolinska Institute (Sweden): rdo@ki.se
- Data Protection Officer of Finnish Institute of Health and Welfare (Finland): tietosuoja@thl.fi
- Data protection officer of the FH Joanneum (Austria): datenschutz@fh-joanneum.at

Please see a more detailed description of the legal basis of personal data processing, of the processing of your data and your rights in the following section.

EU Privacy Regulation 679/2016 the < Add national rules, and *Data Protection Authority>*

Researchers and other members of the study staff are committed to follow Good Clinical Practice (GPC) and research ethical guidelines. Please see a more detailed following:
In this clinical study, the study physician and the site staff will collect and record data relating to you only if this is essential for the conduct the study as described to you or for achieve its objectives.
The information collected by this research project will be kept confidential, except for disclosure under the law or as described in this informed consent form.
You will be provided with an ID code, "subject code" when you enter the study and give you a dummy Lethe Google account in order to protect your identity. The data related to the study will only refer to you using this subject code. The data protected by this ID code is called Pseudo-anonymized.
Your name and contact details will never be made public, only members of the study staff who have signed a confidentiality agreement know your identity.
Only the following people will be able to connect to the Your identity to your subject code at the study center:

- The study doctor and the people with whom he collaborates at the experimental center for the purpose of conducting the study.
- Authorized representatives of the study site who are bound to secrecy, as well as representatives of national and/or foreign health authorities and the relevant ethics committees, may inspect this data insofar as this is necessary or prescribed for checking the proper conduct of the clinical study.

For this reason, it will not be possible to guarantee absolute secrecy. In the unlikely event that security is compromised and your personal data becomes available properties, we will notify you, the data protection

authority and the other partner jointly responsible for the lawfulness of the protection of your personal data.

What data do we collect about you?

By signing this Information Sheet and Informed Consent Form, you acknowledge that the study physician and his staff must collect and use your personal data if you wish to participate in the study. Without these data, the study would have no scientific or clinical value.
The data we will collect includes all the areas listed in the "study procedure" section of this document.
All persons who have access to this data are subject to the applicable national data protection regulations and/or the EU General Data Protection Regulation (GDPR) when handling the data. The code that enables this pseudonymised data to be assigned to you and your dummy Lethe Google account is only kept at your study center.
Only the pseudonymized or anonymized data will be used for any publication of the study results.

How will we protect your data?

In the context of this clinical study only named persons in the research group can process your personal data (persons for whom it is necessary in order to carry out their job tasks).
The data collected from all participants in the study visits and by the Lethe app and passively collected data from extermal apps are stored on a server by EGI foudation (EGI) outside the clinical center till the end of the study period.
As third-party services are also required to conduct this study, such as Google and, Fitbit, you must also agree to their terms of use and privacy policy in order to be able to use the corresponding function.
This study has no influence on the data collection and management of these external companies.
With regard to Google and Fitbit, this is necessary in order to be able to take part in the study; all other third-party functions can be used optionally. Fitbit and Google will not be able to access any of the data entered in lethe app or collected during the visits, but the LETHE team will be able to access the information from fitbit and will also store it in the Lethe server and combine it with all other data collected in the study, for the proposes described in the research plan.
In addition to that, also data (pseudonymized) sources that are transferred to other project partners in order to store and analyse them for future investigations dementia-related (optional for UPG and MUW):

- MRI scan and data of cognitive training will also be stored in Combinostics own server (“West Europe” data centre located in the Netherlands).
- Blood samples will be stored at “Medical University of Vienna” (MUW, Spitalgasse 23, A-1090 Vienna)

Pseudonymized research data (only the necessary data) may also be shared with international collaborators and partners outside the LETHE research group (not all of whom are known yet) for purposes related to research and product development according to the research plan. In this situation, some of the pseudonymized data may be transferred outside EU/EEA to countries where the level of data protection may be lower. LETHE research group will in this case ensure that appropriate and safe measures will be followed when transferring and processing the data and all partners are committed to handle the data confidentially.

How long will your data be stored?

At each clinical site, the Principal Investigator will be responsible for storing and archiving all trial documents. Those will be stored for 15 years following the end of the study at the clinical institutes (KI, MUW, THL and UPG). All persons who have access to this data are subject to the applicable national data protection regulations and/or the EU General Data Protection Regulation (GDPR) when handling the data.
After these the study data will be rendered anonymous or destroyed according to current legislation.

What are the legal bases for processing your personal data?

Processing necessary for the pursuit of the legitimate interest of the data controller (Article 6, paragraph 1, letter e), in conjunction with Article 9, paragraph 2, letter i) or j), GDPR.

What are the rights of the participants?

You can revoke your consent to the collection and processing of your data at any time without justification. If you withdraw your consent to participate in this study, your personal data and study data about you collected prior to such withdrawal may continue to be used as described above. Once you have withdrawn your consent to participate in the study, no further data will be collected on your account for the purposes of this study, unless you decide otherwise, for example, you agree to undergo further tests. If you consent to the collection of additional data after withdrawing your consent, such study data may also be used as described above.
Please note that you have the right to be informed about the processing of your personal data and to request that the processing of your personal data be restricted. You also have the right to review your information and request that it be corrected or supplemented if, for example, you find an error in it or it is incomplete or inaccurate. You also have the right to object to the processing of your personal data. However, in the context of scientific research, these rights may be restricted. The law may oblige the data controller to retain your research data for a certain period of time, regardless of the data subject's rights. The law allows exceptions to the data subject's rights when it is necessary to ensure the results of scientific research and the safety of the subjects. You have the right to receive the information free of charge and within a reasonable time (within one month of the request). If your request for information is very large or for any other justified reason the collection of information takes a long time, the deadline can be extended by a maximum of two (2) months. You will be informed of the extension and the reason for it.
If you wish to exercise these rights or make a complaint, please contact your practice doctor or data protection officer (a staff member at your practice center who is responsible for verifying that personal data is kept confidential).

- XXXXXXXXXXXXXXXXXXXXXX
- The data protection officer for personal data at clinical site is XXX (e-mail address of DPO: xxx)
- contact of national GUARANTOR OF PRIVACY

Part II: CERTIFICATE OF CONSENT

Please see the **ANNEX 10** to this document

5.3.1 Feedback from Advisory Board to main consent form

As also reported in D8.8 "Recommendations on social and ethical implications of the project", four members of the Advisory Board reviewed the main consent form and information sheet and provided feedback in writing.
Several comments and suggestions were related to the amount of information and comprehension of the text, some examples included:

- The information sheet was described long, but members acknowledged the compromise between including enough details and information and the length of the document.
- The amount of information and details that participants would receive was perceived in general as very relevant. Overall members were happy with the amount of detail provided in the information sheet, but some wanted to emphasise the relevance of some parts (e.g. purpose of the study, what is required from each participant and the benefits and risks of participating) or to make more visible some parts of the text which they felt were very important (devices used, number of visits and timeframe etc).
- Another relevant aspect was the way the information was presented, this included the tone (which most members felt appropriate, one thought it was a bit too formal) and the layout. One member made suggestions for including subheadings in the text as this would enhance comprehension and combining two sections which were around a similar topic (voluntariness and right to withdraw).
- Suggestions also included to avoid the use of acronyms (e.g., Principal Investigator in full instead of PI), used the terms consistently (e.g., study, pilot trial) and make sure lay language is used as much as possible. For example, the term "pseudo-anonymized" may not be fully understandable to participants and may cause confusion.
- One of the reviewers made specific suggestions for change in places where the phrasing of the text was unclear or could be improved or was too complicated.
- Different suggestions to improve comprehension were made
    - The participant could test the different devices and apps in advance to the study so to have a better idea of what it involved
    - Additional supplementary information to be provided separately of the informed consent sheet as an "extra information packet"

It was suggested that the contribution that participants can be made was not given enough visibility and relevance: "Through your participation in this study, you can advance aging- and dementia-related medical research" and this should be emphasised as this could motivate participants and should not be presented as something "*small or modest*".
It was welcomed that participants were encouraged to have a study partner but that not having a study partner did not prevent them from participating and it was asked to give more visibility to this.
One member suggested that as the intervention is quite demanding, it should be easy and clear to participants how to stop their participation at any point if the so wished. It was also suggested that to avoid drop outs the study should be flexible and accommodate to participants needs.
It was suggested that it would be best if there was some information available in the Lethe website in all the different languages and not just in English ("A description of this clinical trial will be available on the website "www.lethe-project.eu". The website will not contain information that can identify you. At most, the website will present a summary of the results. You can consult the website at any time. This website may only be available in English; if you need assistance, talk to your doctor at study site"

Conclusion of the AB
Information is key for promoting the autonomy of participants and ensuring that there is an informed decision to join (or not to join) the study. This information had different components such as information prior to joining the study about what is expected from them and what this entails, during the study in relation to their progression and how this is impacting on their risk, and at the end of the study about the study results. Information should be accessible, appropriate, respectful and tailored to the participants' needs and wishes.

Implementation of these suggestions:

- Emphasize the concepts indicated by the AB in the consent form also through the font of the text and the size of the characters.
- Modify in the text the acronyms and use the same term through the text for indicate the pilot trial.
- Add, at the end of the consent form after the signature of the subject, the sentence: "Thank you for your participation and your contribution to scientific research!
- Develop a small brochure or guide on devices and apps for the users.
- Provide a short lay summary of the main findings on the project website in all four local languages of the clinical centers.

5.4 Information sheet and informed consent form for the study partner

GENERAL INFORMATION AND PURPOSE

Research has shown that a healthy lifestyle, including a balanced diet, physical and social activity, and management of vascular risk factors (e.g., blood pressure, cholesterol) can support both cardiovascular and brain health. In a landmark Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), a multimodal lifestyle program had clear benefits on older adults' memory, functioning, and quality of life. More research is needed on whether and how such a lifestyle program could be delivered with the help of new digital tools, such as smartphone and mobile applications.

The main objective of this clinical study is to assess the feasibility of a digitally delivered lifestyle program to support active and healthy ageing in older adults. We will assess how well participants adhere to the lifestyle program and the digital solutions offered to them. We will also assess how participants' lifestyle (e.g., diet and physical activity) and their risk of developing dementia based on validated risk scores change over time. Other objectives in the LETHE project include investigating and identifying risk and protective factors and mechanisms related to healthy aging and cognitive decline, using also machine learning based approaches.

SELECTION OF PARTICIPANTS

The LETHE pilot trial will be conducted at four European study sites (Medical University of Vienna in Austria, Finnish Institute of Health and Welfare in Finland, University of Perugia in Italy, and Karolinska Institute in Sweden). A total of approximately 160 participants will be recruited. In Finland/Sweden/Italy/Austria, we will recruit approximately 40 persons. We will invite older adults aged 60-77 who do not have any substantial cognitive impairment but have some risk factors for cognitive decline. These include education level, systolic blood pressure, total cholesterol, body mass index, and level of physical activity. Participants should also be able and willing to use an Android smartphone to follow lifestyle advice given in the trial and to fill in questionnaires.

VOLUNTARY PARTICIPATION

It's your choice to decide whether to participate in the study with the subject. The doctor/site staff will describe the study to you and review this information with you and the subject, and it will be to you provided a copy of this form to take home with you. If you agree to participate, the doctor/site staff will ask you to sign and date this consent form. You can choose not to participate in the study and will not have to justify your decision. The assistance the subject receives will not be compromised; the subject can participate even if he is unable to name any person. If you choose to participate, you can change your mind at a later time and stop participation at any time, for any reason, without giving explanations.

STUDY PROCEDURE

Before carrying out any study-related procedures, you will be required to sign / date this consent document.

The duration of the study is 24 months for each participant. You will be invited to attend two main study visits at the study center: baseline (at beginning of the study) and at 24 months (end of the study). Each visit will last approximately 4-5 hours, and assessments can be completed during one day or split over several days. You do not need to be present during the entire study visit, the testing that requires your assistance will take about 40 minutes, or you can also be interviewed e.g., over the phone/ video.

You will be asked to help answer questions that require general information, the subject's health conditions and habits. During the Baseline visit and Month 24 assessment visit, you will be asked questions about any changes in subject's memory and health. Your responses will be noted. You and the subject will be interviewed separately. This helps ensure an evaluation complete and independent.

EXPECTATIONS

If you participate in this study, the following is expected: Accompanying the subject to visits which include your presence, it will be the duty of the study's staff to provide a reminder of the appointment. Answer sincerely and truthfully the questions that the study staff will ask you about any changes in memory and health. Also, general information, the health conditions of the subject and habits. Your answers will be noted.

STUDY PROCEDURES IN THE CONTEXT OF THE COVID-19 PANDEMIC

The interventions have been planned to be partly deliverable in a remote setting can be conducted via a video call. In these cases, visits that may not be conducted in person at the study site at the scheduled time (due e.g., COVID-19 related restrictions or other travelling difficulties) will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits are possible.

RISKS ASSOCIATED WITH THE STUDY PROCEDURES

If you participate in this study, you will have to devote some of your time to it and this could be an unease. The doctor/study staff will ask you a few questions on the subject. He may feel uncomfortable in answering some of these questions, but it is important that you answer them in the sincerest way as possible.

COSTS FOR THE STUDY PARTNER

You will not be charged any costs for materials, visits, or any study-related procedure performed during this study. You will not receive any compensation for participating in this study.

SHORT DESCRIPTION OF PROCESSING OF PERSONAL DATA AND ITS CONFIDENTIALITY

This study follows XXX data protection regulation. Researchers and other members of the study staff are committed to follow good clinical practice and research ethical guidelines.

The study is conducted by <Clinical Partner name>. The Principal Investigator is < Name of clinical center PI>. The Principal Investigator in <Country> with responsibility for the safety of xxx participants is <Name>.

Medizinische Universität Wien (MUW), Universita degli Studi di Perugia (UPG), Karolinska Institutet (KI), Finnish Institute for Health and Welfare (THL), FH JOANNEUM and Combinostics Oy (COMB) as “data Controller” are responsible for the lawfulness of the processing of personal data in the context of the study.

Extra Red Srl (ER), Infotrend Innovations Company Limited (INFO), Idryma Technologias Kai Erevnas (FORTH) and EGI Foundation (EGI) as “processors” play a role in the processing of your data and have accepted a data processing agreement aimed at ensuring that personal data is not processed illegally, wrungfully or processed in way that results in unauthorized access, alteration, erasure, damage, loss or unavailability.

IPHC / SCIGNE platform. Fitbit (FB), Kaasa Solution GmbH (KA) and Google are defined as "sub-processors" and are hired by processors to carry out specific Processing activities on behalf of the Data Controllers.

Study is funded by the European Union’s Horizon 2020 research and innovation programme under grant agreement no 101017405.

PRIVACY

As part of this clinical study, no sensitive data concerning you will be collected. The only personal data that will be recorded are your name, the type of relationship with the subject of the study and your phone number. This data will be stored at the center until the end of the project in a safety place with limited access only to authorized person, after these, the site will proceed to destruct it according to the regulations in force. The only other data collected is yours answers to questions relating to the subject, which will be noted as specified previously. This informations will be stored in a server by EGI foudation (EGI) outside the clinical center till the end of the study period. Subject received information about the data that will be collected and has accepted such collection. The doctor/site staff will ensure that all information about you is handled confidentially. They will refer to you using a code when you are enrolled in the study and the information that you report will be protected. Yours name and contact details will never be made public. At each clinical site, the Principal Investigator will be responsible for storing and archiving all trial documents. Those will be stored for 15 years following the end of the study at the clinical institutes (KI, MUW, THL and UPG) in accordance with the GDPR.

Under the law of the European Union, you have various rights regarding data protection. If you believe that these rights have been violated or if you have any concerns about privacy or the confidentiality of your documentation during the study, you can contact:

- Add Site Contact
- The data protection authority (GUARANTOR OF PRIVACY)

11. SHARING OF RESULTS

The results of this study could be published in a medical journal or technology and presented in scientific congresses. You will not be identified (with your name or any other way) in any of these publications.

12. RIGHT TO REFUSE OR WITHDRAW

You are not obliged to participate in this research if you do not wish to do so. It can also interrupt participation in the research at any time without explaining. If you want to stop participating, we will use all data collected up to the time you stop the participation. It is your choice, and all your rights will be respected. The subject's future standard of care will not be compromised. Furthermore, if another partner of the study has provided written consent to participate and assume the necessary responsibilities, he can replace you if you decide not to participate in the study anymore.

If you have any questions about this research or this study, or in case of any problems, doubts, complaints, you can contact your doctor's office at the telephone numbers listed below.

• Add contact

CERTIFICATE OF CONSENT

Please see the **ANNEX 11** to this document.

6 Optional future biological research

The study protocol stipulates that at the Baseline, visit together with a Routine blood tests (total cholesterol, HDL, LDL, triglycerides, HbA1c, CRP, fasting glucose, creatinine, ASAT, ALAT, GGT) blood samples will also be collected for the determination of apolipoprotein E (APOE) genotype and other genetic factors on dementia-related blood-based biomarker studies (e.g., AD markers pTau, neurofilament light chain, and genetic factors), and some blood will also be fast frozen and stored for research purposes in the future investigations. One serum tube will be sent to MUW to measure potential serum biomarkers of AD pathology with SIMOA technology.

For the THL and KI clinical centers, the storage of blood samples for future biological research is not an optional procedure therefore subjects who agree to participate in the main study by signing the consent also agree to participate in these future studies on dementia-related blood-based biomarker studies. This is a legitimate interpretation of the GDPR and of the use of the public interest as a legal basis for the data processing, including genetic data.

However, in Italy and Austria the local ethics committee recommends to use “the consent” as legal bases for this type of data processing and produce an informed consent form for the genotyping sub-study to which subjects must explicitly consent to participate and authorize future biological research. For this reason, a separate form **(ANNEX 12)** has been produced to submit to the ethics committee for approval along with all other consent forms.

ANNEX

ANNEX 1: LETHE INVESTIGATOR SIGNATURE SHEET

By singing below, the Principal Investigator of the site (clinical center), are agrees to conduct this study as set out in the study protocol in force and subsequent updates.

I (PI's name) _____ agree to conduct this study according with the ethical standards and guidelines of Horizon 2020, including the Charter of Fundamental Rights of the European Union and the European Convention on Human Right. Medical research in human subjects will follow the procedures described in the World Medical Association's Declaration of Helsinki and the Oviedo Bioethics Convention (Convention on Human Rights and Biomedicine). In addition, all procedures will comply with National law and the European Union's General Data Protection Regulation (GDPR). Relative procedures will follow the ICH Guidelines for Good Clinical Practice E6(R2) and the Good Clinical Practice Directive 2005/28/EC."

I fully understand that any changes instituted by me without previous discussion with Lethe consortium constitute a deviation from the protocol.

I agree to adhere to the protocol in all circumstances other than where necessary to protect the well-being of the subject.

Study Site Principal Investigator

Name:

Title:

Address:

Contact:

Signature:

Date:

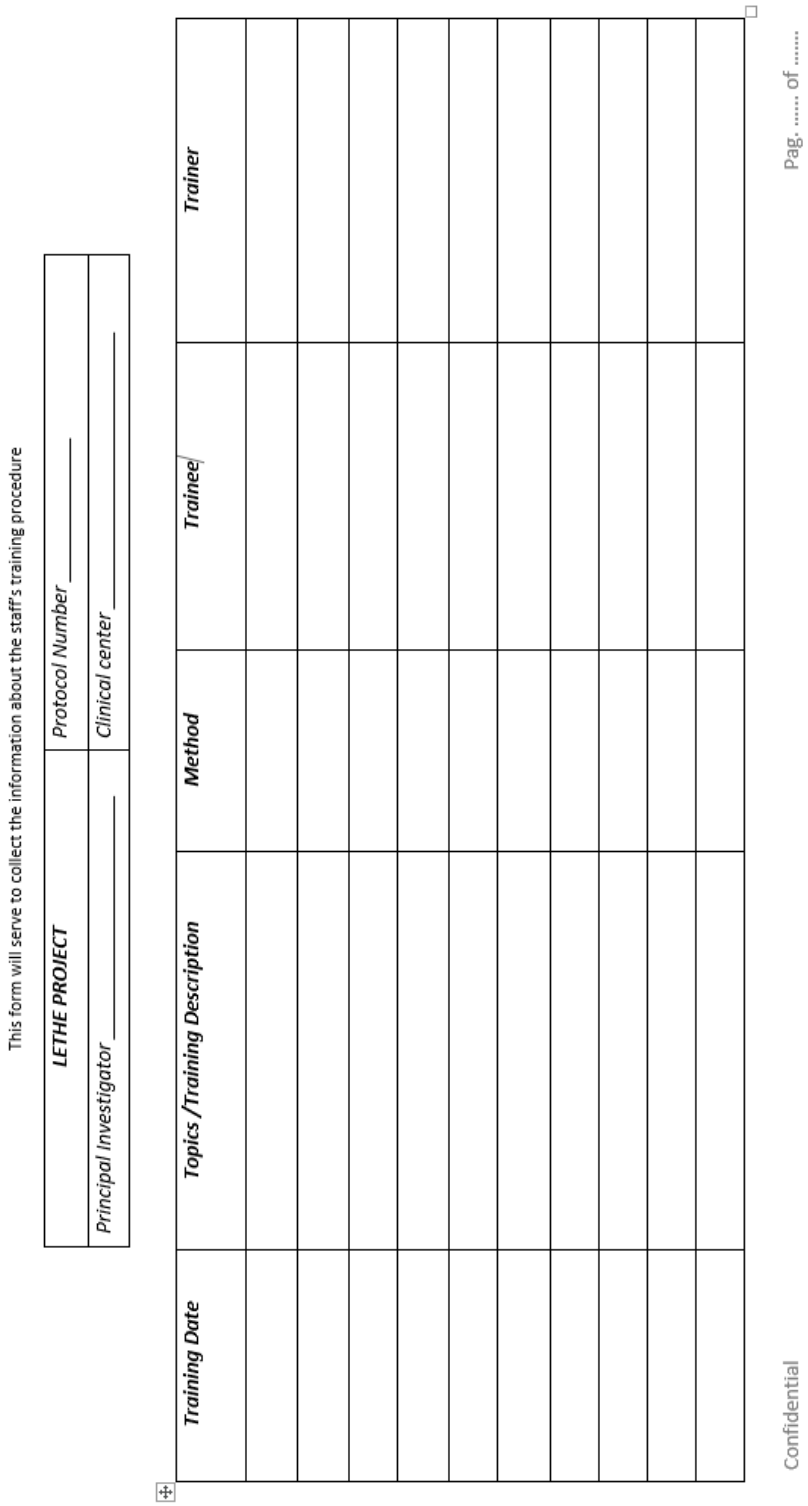
ANNEX 2: LETHE SITE'S TEAM FORM

This form will serve to collect the information about the personnel of the site involved in the study protocol, their authorization to perform studies procedure and contact information.

LETHE PROJECT	
Principal Investigator _____	Protocol Number _____ (and above) Clinical center _____

NAME	STUDY ROLE	CONTACT	SIGNATURE	START Date	PI's initials and date	END Date	PI initials and date

ANNEX 3: LETHE STAFF TRAINING LOG



This form will serve to collect the information about the staff's training procedure

LETHE PROJECT	*Protocol Number* _____
Principal Investigator _____	*Clinical center* _____

Training Date	*Topics /Training Description*	*Method*	*Trainee*	*Trainer*

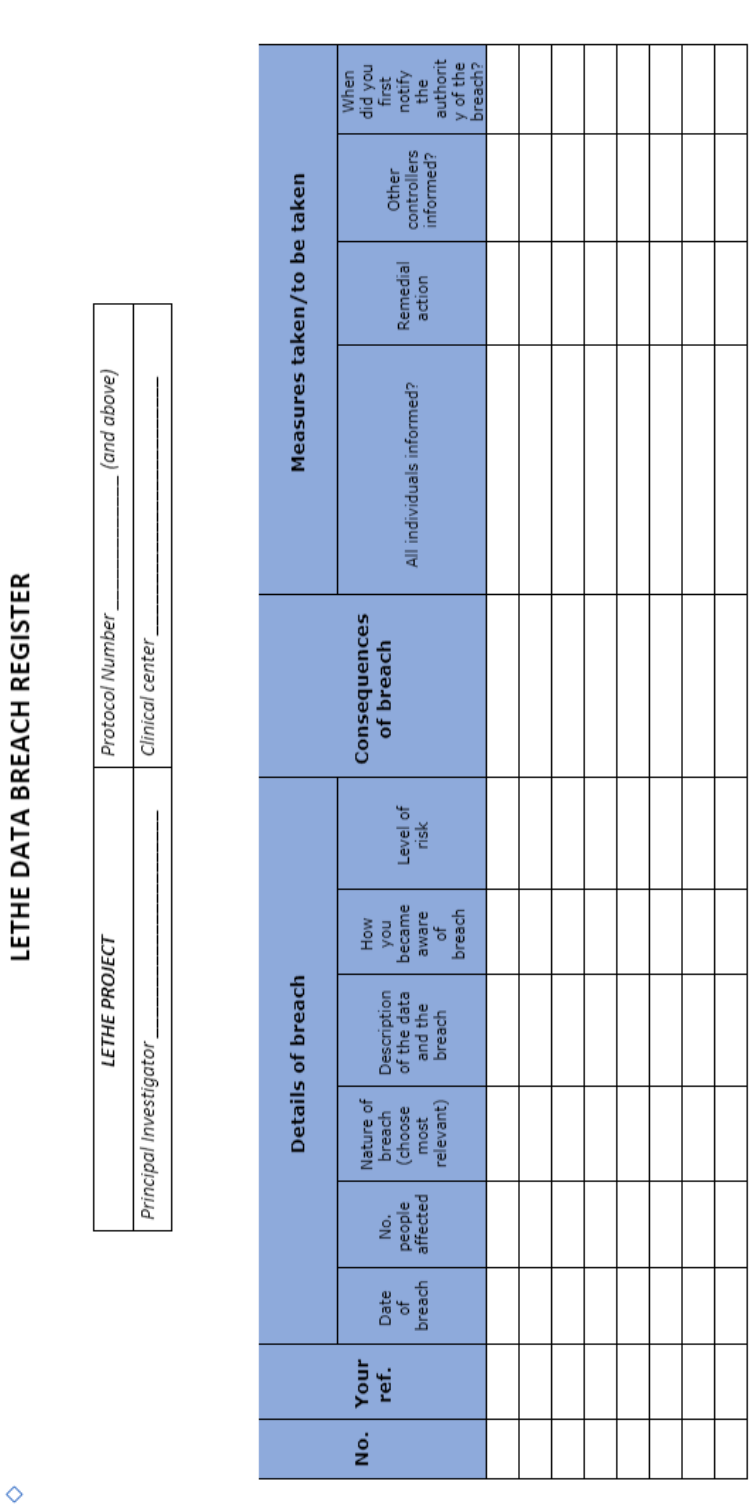
Pag. ..... of .....

Confidential

ANNEX 4: DATA BREACH NOTIFICATION TO DATA SUBJECTS

Notification of Data Security Breach	
Date(s) of Breach:	
Date Incident was discovered	
Name of Person Reporting Incident	
Contact Details of Person Reporting Incident	
Brief Description of Personal Data Security Breach	
Number of Data Subjects affected if known:	
Brief Description of any action since breach was discovered	
Report sent by:	
Date:	

ANNEX 5: DATA BREACH REGISTER



LETHE DATA BREACH REGISTER

LETHE PROJECT	*Protocol Number* _____ *(and above)*
Principal Investigator _____	*Clinical center* _____

No.	Your ref.	Details of breach							Consequences of breach	Measures taken/to be taken			
		Date of breach	No. people affected	Nature of breach (choose most relevant)	Description of the data and the breach	How you became aware of breach	Level of risk		All individuals informed?	Remedial action	Other controllers informed?	When did you first notify the authority of the breach?

ANNEX 6: DATA SUBJECT ACCESS REQUEST FORM

You have the right to request for personal data we may hold about you. This is known as a Data Subject Access Request ("DSAR"). A data subject is an individual who is the subject of the personal data. If you wish to make a DSAR, please complete this form and return to us by post or email.
If sending by post, please use the following address: Lelia Ataliani Infotrend Innovations Co Ltd 13 Demonaktos str. 1017 Nicosia- Cyprus
If sending by email, please use the following address**: lelia@infotrendco.com** Please write "Data Subject Access Request" in the subject field of the email.

1. Data Subject's Full Name	**2. Data Subject's Date of Birth**

3. Data Subject's Current Address

4. Data Subject's Telephone Number	
Home Telephone No:	Mobile Telephone No:

5. Details of data requested: **To help us search for the information you require, please let us know the data you require with as much detail as possible (e.g. copies of emails between <date> and <date>). If we do not receive sufficient information to locate the data you require, we may be unable to comply with your request.**

6. Is the information going to be sent to the data subject or his/her representative?
To the data subject ☐ To the representative ☐ If the data is sent to the representative, then sections 9 and 10 need to be filled out.
7. I confirm that I am the Data Subject.
Signature: _____ Print Name: _____ Date: _____ I enclose a copy of my ID and address proof documents (including a government issued ID document).
8. (To be filled out if the question 7 is answered with "To the representative") The Data Subject (whose data is being requested) must give written authorization for the information to be released to his/her authorized representative.
I hereby give my authorization for _____ (fill out the name of the authorized representative) to request access to my personal data. Signature of Data Subject:_____ Print name: _____
9. (To be filled out by the representative of the data subject) I confirm that I am the authorized representative of the Data Subject.
Name of authorized representative (capitol letters) _____

Address where personal data is to be sent:

_____

Signature: _____

Print Name: _____

Date: _____

We will make every effort to process your data subject access request as quickly as possible within 30 working days. However, if you have any queries whilst your request is being processed, please do not hesitate to contact the doctor responsible for the study protocol at the clinical center: [email and contact details]

ANNEX 7: DATA SUBJECT CONSENT WITHDRAWAL FORM

I, _____ [subject name], would like to withdraw my consent to process my personal data within the Lethe research project. Thus, Lethe's data controller and data processors no longer has my consent to process my personal data of for the proposal of the project which was previously granted using the "MAIN INFORMATION AND INFORMED CONSENT FORM FOR THE SUBJECT."

The withdrawal of consent does not affect the lawfulness of the processing activities up to this point.

Signed by data subject:

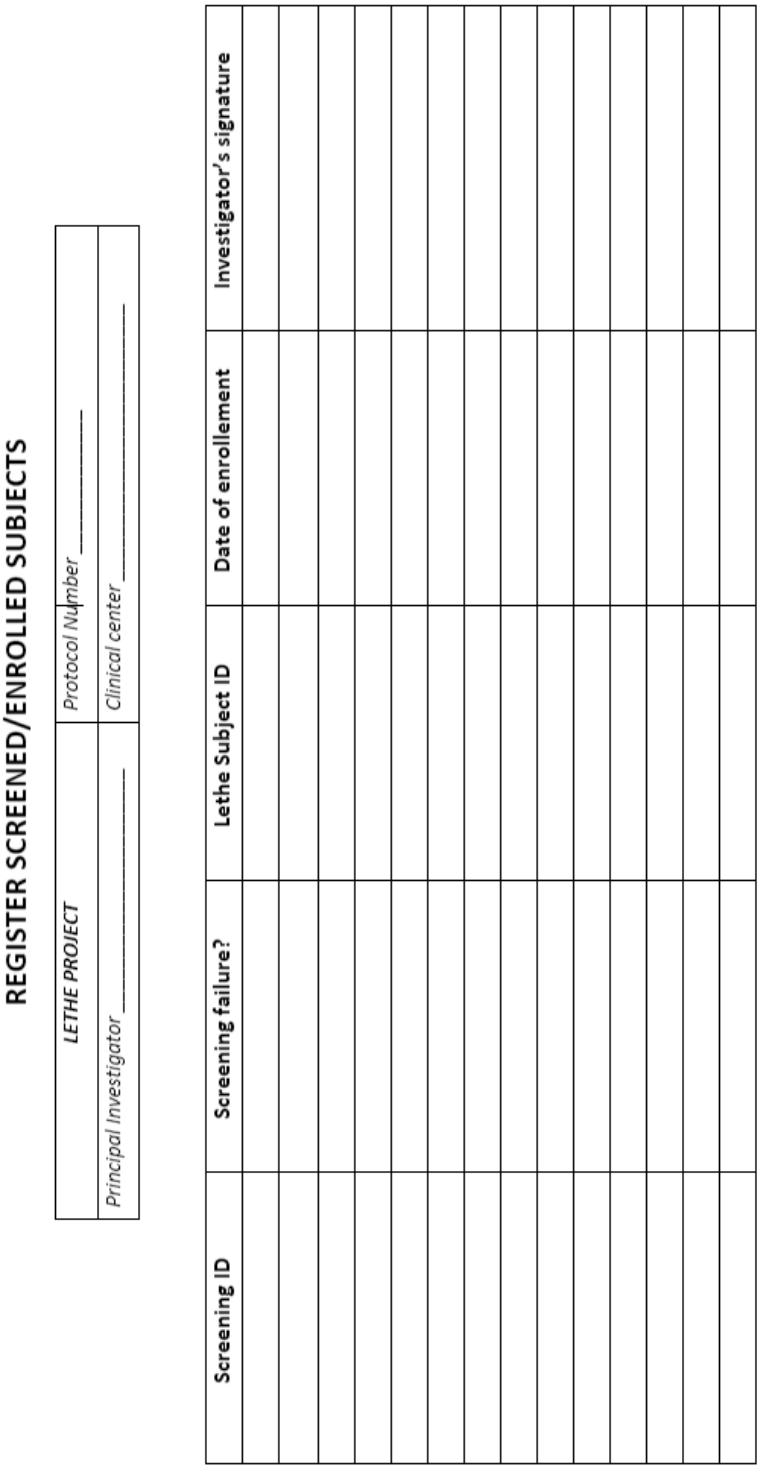
Name and surname in capital letters:

_____

Signature: Date:

_____ _____

ANNEX 8: REGISTER SCREENED/ENROLLED SUBJECTS



REGISTER SCREENED/ENROLLED SUBJECTS

LETHE PROJECT	*Protocol Number* _____
Principal Investigator _____	*Clinical center* _____

Screening ID	Screening failure?	Lethe Subject ID	Date of enrollement	Investigator's signature

ANNEX 9: Template of "INFORMED CONSENT FORM FOR THE SCREENING PROCEDURE"

I ……..(participant name)
have been invited to participate in the screening assessment for the above-mentioned clinical study which aims to assess the feasibility of a digitally delivered lifestyle program in supporting brain health in older adults.
I have read and understood the information sheet concerning the screening assessment. I have received enough information about the screening procedure and the related data collection, processing and storage. The content of the information sheet has also been explained to me verbally and all my questions have been answered.
I have had enough time to consider potential participation. I have received enough information about how the purpose and execution of the study, its potential benefits and risks, and my rights as a participant. My participation is voluntary, and I have not been pressured to make a decision. I am aware that I will not receive any financial compensation or reimbursement for the participation.
I am aware that my personal data is processed confidentially and will be shared within the LETHE research group. Pseudonymized data will be shared and analyzed within the LETHE study group among the involved partners as described in the research plan. Pseudonymized research data may also be shared with international collaborators and partners outside the LETHE research group (not all of whom are known yet), for research purposes outlined in the research plan. In this situation, some of the pseudonymized data may be transferred outside EU/EEA to countries where the level of data protection may be lower. LETHE research group will in this case ensure that appropriate and safe measures will be followed when transferring and processing the data and all partners are committed to handle the data confidentially.

I am aware that I have the right to refuse participation. I can also later on withdraw my consent at any time without giving any reason, and it will not affect my current or future medical care in any way. I am aware that if I withdraw my consent, any data and samples collected so far will be used as part of the research project.

Please check the box below if you intend to provide your consent to be contacted for any sub-studies related to this or for new research and prevention projects in order to support brain health in older adults

o I AGREE TO BE CONTACTED

"I AGREE TO PARTICIPATE IN THE SCREENING VISIT DESCRIBED ABOVE"

_____
Name and surname of the subject (CAPITAL LETTERS)

_____ _____
Signature of the subject Place and date

_____
Signature of person who conducted the information consent interview at the site

ANNEX 10: Template of "MAIN INFORMATION AND INFORMED CONSENT FORM FOR THE SUBJECT"

I .....(participant name)
have been invited to participate in the "LETHE" project for the above-mentioned clinical study which aims to assess the feasibility of a digitally delivered lifestyle program in supporting brain health in older adults.
I have read and understood the information sheet concerning the study assessment. I have received enough information about the study and the related data collection, processing and storage. The content of the information sheet has also been explained to me verbally and all my questions have been answered.
I have had enough time to consider potential participation. I have received enough information about how the purpose and execution of the study, its potential benefits and risks, and my rights as a study participant. My participation is voluntary, and I have not been pressured to make a decision. I am aware that I will not receive any financial compensation or reimbursement for the participation.
I am aware that my personal data is processed confidentially and will be shared within the LETHE research group. Pseudonymized data will be shared and analyzed within the LETHE study group among the involved partners for purposes related to research and product development according to the research plan. Pseudonymized research data, only the necessary, may also be shared with international collaborators and partners outside the LETHE research group (not all of whom are known yet), for research purposes outlined in the research plan. In this situation, some of the pseudonymized data may be transferred outside EU/EEA to countries where the level of data protection may be lower. LETHE research group will in this case ensure that appropriate and safe measures will be followed when transferring and processing the data and all partners are committed to handle the data confidentially.
I am aware that I have the right to refuse participation. I can also later on withdraw my consent at any time without giving any reason, and it will not affect my current or future medical care in any way. I am aware that if I withdraw my consent, any data and samples collected so far will be used as part of the research project.

OPTIONAL	Yes	No
I would like to be contacted for a possible optional qualitative substudy on my experiences in the main study and with the LETHE app (e.g. usability, accessibility, technical aspects).		
I would also like to be contacted regarding participation in other possible sub-studies of this study.		
I agree to be re-contacted later regarding other potential aging or dementia related clinical studies.		

"I AGREE TO PARTICIPATE IN THE STUDY DESCRIBED ABOVE"

_____ _____
Signature of the subject Place and date

_____
Name and surname of the subject (CAPITAL LETTERS)

_____
Signature of person who conducted the information consent interview at the site

_____
Place and date

_____
Name and surname of the person who conducted the informed consent interview (CAPITAL LETTERS)

Thank you for your participation and your contribution to scientific research!

ANNEX 11: Template of “INFORMED CONSENT FORM FOR THE STUDY PARTNER”

I confirm that I have read Part I, the information sheet, for this study. I have had the opportunity to review the information and ask questions and I received satisfactory answers. I am aware that my participation in this study as a “person who knows well the subject” is voluntary and that I am free to withdraw at any time without providing no justification.
I understand my roles and responsibilities in the study for the purposes of this study, and I agree to play this role for the number identification of the subject _____

"I AGREE TO PARTICIPATE IN THE STUDY DESCRIBED ABOVE"

_____ _____
Signature Place and date

_____
Name and surname of the partner (CAPITAL LETTERS)

_____
Signature of person who conducted the information consent interview at the site

_____
Place and date

_____
Name and surname of the person who conducted the informed consent interview (CAPITAL LETTERS)

ANNEX 12: INFORMATION SHEET AND INFORMED CONSENT FORM FOR THE FUTURE BIOLOGICAL RESEARCH – OPTIONAL

You have been invited to participate in a Future Biological Research sub-study. The decision of it is up to you to participate in the study. The doctor / study staff will review this information with you. If you agree to participate, you will be asked to sign this consent form. Can decide immediately not to participate in this research or you can decide to participate and then change your mind without having to provide a justification. This will not affect the standard of care he receives.

If you do not wish to have this blood test, this will not prevent you from participating in this study.

If you adhere to this optional research, together with the blood sample for the blood tests provided for in this study protocol, an additional sample tube (7 ml) will be taken from you at the same time of routine blood test scheduled for the main study, fast frozen and stored for future investigations on dementia-related blood-based biomarker studies. There are no additional risks for the participant. There are no costs related to this procedure and there is no compensation for your participation in this sub-study.
This blood collected for future biological research will be frozen and stored for subsequent analysis of various biomarkers and genetic factors related to aging and dementia with the data collected in this study to advance scientific and public health research. Any residual samples from these tests can be stored and examined for the search for proteins or other substances that are still unknown but which could become very important with the progress of scientific research in this topic. Neither you nor the doctor /site staff you will receive the results of these future tests and the results will not be included in your medical information.

Your samples will be stored frozen at “Medical University of Vienna” Spitalgasse 23, A-1090 Vienna afterwards the end of this study until the samples have been fully used. This laboratory is experienced in handling samples from research studies, under close supervision and with limited access in order to keep blood samples safe and secure. Your samples will be tagged with a code in order to protect your identity. All information relating to these samples will be managed with the same procedures used for all other personal data concerning you. The link between the sample id and your identification number of the subject participating in the main study will be kept in a secure location at the clinical center, with limited access.

Medizinische Universität Wien (MUW), Universita degli Studi di Perugia (UPG), Karolinska Institutet (KI), Finnish Institute for Health and Welfare (THL), FH JOANNEUM and Combinostics Oy (COMB) as “data Controller” are responsible for the lawfulness of the processing of personal data in the context of the study.

Extra Red Srl (ER), Infotrend Innovations Company Limited (INFO), Idryma Technologias Kai Erevnas (FORTH) and EGI Foundation (EGI) as “processors” play a role in the processing of your data and have accepted a data processing agreement aimed at ensuring that personal data is not processed illegally, wrungfully or processed in way that results in unauthorized access, alteration, erasure, damage, loss or unavailability.

IPHC / SCIGNE platform. Fitbit (FB), Kaasa Solution GmbH (KA) and Google are defined as "sub-processors" and are hired by processors to carry out specific Processing activities on behalf of the Data Controllers.

Study is funded by the European Union’s Horizon 2020 research and innovation programme under grant agreement no 101017405.

If you withdraw your consent to participate in the main study, your samples collected prior to such withdrawal may continue to be stored and analyzed as described in this information sheet.

You can withdraw your consent to the use of your samples in future research at any time: if you withdraw your consent after a sample has been collected but before it is sent to the laboratory in charge of storage, the investigator of the center will have it destroyed the samples in accordance with the regulations in force. However, if the sample has already been used for biological research, the Lethe consortium shall not be required to destroy the results of the research but only eventual residual samples, unless the sample ID has been removed and it can no longer be linked back to you.
If you wish to exercise these rights or make a complaint, please contact your site doctor or data protection officer:

- Xxxxxxxxxxxxxxxxxxx
- Data Protection Officer

According to the EU Data Privacy Regulation 2016/679, the Protection Code data (Legislative Decree No. 196/2003 updated by Legislative Decree No. 101/2018), of the General Authorization for the Processing of Genetic Data of 22 February 2007 e of the General Authorization n. 8/2016 for the processing of genetic data dated 15 December 2016 issued by the Italian Guarantor for the protection of personal data and subsequent amendments.

CONSENT FORM FOR THE FUTURE BIOLOGICAL RESEARCH

I confirm that I have read the Information Sheet, for this sub study. I got to reflect on the information and to ask questions and I received satisfactory answers. I am aware that my participation is voluntary and that I am free to withdraw in any time without having to provide a justification and without my medical treatment or my legal rights are compromised.
Please mark your choice for optional future biomedical research on biological samples.

□ **YES,** I agree to the use of my unused samples for future biomedical research

□ **NO**, I do not consent to the use of my unused samples for future biomedical research

_____ ----------

-

Name and surname of the subject (CAPITAL LETTERS) Place and date

_____

Signature of the subject.

_____

Name and surname of the person who conducted the informed consent interview (CAPITAL LETTERS)

_____

Place and date

_____

Signature of person who conducted the information consent interview at the site