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
H2020-SC1-DTH-2020-1
GA 101017405

Duration: 48 months from 01/01/2021
Coordinator: Sten Hanke, FH JOANNEUM GESELLSCHAFT MBH

Deliverable ID.:	**D8.8**	
Deliverable title:	**Recommendations on social and ethical implications of the project**	
Planned delivery date:	30/06/2022 (M18)	
Actual delivery date:	29/06/2020 (M18)	
Editor:	Ana Diaz (AE) Dianne Gove (AE) Soraya Moradi (AE) Daphne Lamirel (AE)	
Contributing partners:	KI, MUW, THL, UPG, MU	
Internal reviewer:	Patrizia Mecocci (UPG)	
Checked and released by:	Sten Hanke (FHJ)	
Dissemination Level:	**X**	PU = Public;
		CO = Confidential
Type:	Report	

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No. 101017405.

Document information and history

Deliverable description (from DoA)

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

Release number	Release date	Author [Person and Organisation]	Milestone*	Release description /changes made
V. 1.1	01/06/2022	Ana Diaz, Alzheimer Europe	Table of Contents and introduction	Changes in the structure and inclusion of brief ethics section in the introduction
V. 1.2	13/06/2022	Ana Diaz, Alzheimer Europe	Intermediate	Additional points and clarifications to be included in the feedback from Advisory Boards
V. 1.3	22/06/2022	Ana Diaz, Alzheimer Europe	Proposed	Changes in some of the headings to better reflect the content of text and small editing changes. Addition of a new article for the introduction
V. 1.4	27/06/2022	Ana Diaz, Alzheimer Europe	Revised	No changes required
V. 1.5	28/06/2022	Ana Diaz, Alzheimer Europe	Approved	

** 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 new version in response to internal reviewer comments*
- *Approved: Internal project reviewers accept the document.*

Table of Contents

1 Executive Summary

Around 8 million people are currently living with dementia in the European Union. The numbers of people with dementia in Europe will almost double by 2050. Dementia is a major cause of disability and dependency and one of the most feared diseases of ageing. Dementia remains a non-curable disease. However, over the last decades, our knowledge of the risk factors (modifiable and non-modifiable) and the potential prevention of cognitive decline and dementia has significantly improved. 12 risk factors have been identified which might reduce prevent or delay up to 40% of dementias globally.

LETHE is a Horizon-2020 project designed to prevent cognitive decline in older adults by a multi-domain interventional lifestyle approach built on a person-centred digital solution. Lethe is based on an existing, well-known intervention for dementia risk reduction: FINGER "Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability". The Lethe study will help to understand how some parts of the FINGER intervention could be implemented and measured using existing technology. The study will be carried out in 4 different countries and will involve older adults at risk but cognitively healthy. The Lethe study is therefore very relevant and its findings may be very beneficial for a population which is growing older, where fewer resources are available and after the COVID pandemic, where we learned about the difficulties of continuing with a healthy life during confinement and social isolation. However, this approach also raises ethical and social issues. This deliverable presents some of the ethical and social issues of relevance to the Lethe study and provides some recommendations for the different researchers involved in the design, planning, conduct and reporting of the study. The recommendations have been developed based on the input of members of the public (Advisory Board) who have been contributing to different aspects of FINGER and Lethe. Members of the Advisory Board have also provided feedback to this work which was included in the final set of recommendations. The recommendations are grouped around four main topics:

- Providing information and promoting a clear understanding of the intervention and its possible implications.
- Offering support and protecting participants from harmful or burdensome situations.
- Ensuring that the study objectives meet participants' needs in a real-world context and after completion of the study.
- Addressing inequality in access and safeguarding a diverse, non-stigmatising and inclusive environment.

The ethical and social issues related to the project will continue to be addressed in the ongoing meetings of the Advisory Board and reported and addressed in the Public Involvement deliverables of the project.

2 About this Document

2.1 Role of deliverable

The aim of this Deliverable (D8.8) is to consider and present some of the ethical and social issues of relevance to the Lethe project and study and to provide some recommendations for the different researchers (including clinical and technical partners) involved in the design, planning, conduct and reporting of the study

The whole issue of data protection (including legal issues and GDPR) and the scientific validity and appropriateness of the design and methods etc., adopted in Lethe, are not addressed in this document.

The ethical and social consideration of a project like Lethe do not stop after the first months of the project, but are ongoing and should be continually discussed and addressed. This will be the case in Lethe. This report introduces some of the initial considerations, but future meetings of the Advisory Board will continue addressing other topics which will be included in the Public Involvement Deliverables (D8.6 and D8.7).

2.2 Relationship to other Lethe deliverables

This deliverable is related to the following deliverables:

- D6.3 [M18] – Privacy and legal framework I.
- D7.1 [M18] - Study protocol, Description of the detailed study protocol.
- D7.2 [M18] - Ethical Committee approval, Ethical approvals from all 4 evaluation study sides.

In months 24 and 48, Alzheimer Europe will produce Deliverables on the PPI activities conducted in the project. These deliverables, may include other relevant ethical and social considerations addressed by the Advisory Board in future meetings (e.g. after the submission of D8.8). These deliverables will also provide a more detailed description of the composition, methodology and other relevant aspects of the Advisory Board.

- D8.6 [M24] – Report on PPI activities and impact I (AE), This deliverable provides a report I of the activities regarding Public and Patient Involvement.
- D8.7 [M48] – Report on PPI activities and impact II (AE), This deliverable provides a report I of the activities regarding Public and Patient Involvement.

2.3 Structure of the document

This document includes the following parts:

- Introduction to the concepts of ethics, risk, use of technology by older adults and how these relate to the Lethe project.
- The Advisory Boards and approach taken to collect their feedback
- Summary of the feedback provided by the Advisory Boards
- Recommendations

3 Introduction

3.1 Understanding of ethics for this report

Broadly speaking, ethics is a branch of philosophy which seeks to address issues related to concepts of right and wrong (Alzheimer Europe, 2010). It refers to standards which tell us how we ought to act in various situations and how we ought to live with one another. This is often framed in terms of rights, obligations, duties, benefits to society, fairness or specific virtues. These standards of behaviour are based on perceptions of right and wrong or good and bad. Ethics is not just about big societal issues like immigration, war or euthanasia that are discussed in the media. Everyday matters, as well as actions and decisions made by researchers, policy makers and healthcare professionals, can also have an ethical dimension. How these issues are approached by individuals, groups and societies may have implications for how we see ourselves. Behaving ethically in all domains requires a lot of reflection and a willingness to question a lot of the things that we take for granted (e.g. when we sometimes think “that’s just the way it is” or that “it has always been like that”).

To help us weigh up the right way to act, we can consider general principles such as autonomy (being independent and able to decide what should happen or be done to you), beneficence (doing good), non-maleficence (avoiding harm) and justice or equity (treating people equally and fairly). These were initially developed in the context of medical care and treatment and have since been applied in a wide range of social contexts. The relevance of these principles for research has been well described in several key documents such as the Nuremberg code, the Declaration of Helsinki or the Belmont Report.

These principles are based on the recognition that people have rights (e.g. to decide for themselves, to be treated fairly and not to be harmed). There are other principles and values which are equally important in both medical and non-medical settings, including for example trustworthiness, honesty, integrity, compassion, promoting wellbeing, confidentiality and respect for privacy, personhood and dignity.

The four principles (autonomy, beneficence, maleficence and justice) will be used in the current report as the basis to reflect about different issues in the Lethe project and study. Whilst presented here independently, these principles interact and often impact on each other. Principles and interests often complement or sometimes compete and conflict with one another in various ways.

Autonomy

The principle of autonomy is generally linked to self-determination and exercising choice. Respect for autonomy is usually described as “the right of competent adults to make informed decisions about their own medical care”. In research, this principle is related to the autonomy or ability of the participant to make his/her own decisions, and such decision to be recognized and respected, while also protecting the autonomy of the vulnerable participants by preventing the imposition of unwanted decisions (Owonikoko 2013). It comprises two distinct principles: firstly, that participants should be treated as autonomous and secondly, that participants with diminished autonomy should be entitled to additional protections. This principle gave life to the practice of informed consent whereby the participant (or sometimes a legally authorized representative) is allowed to make an informed decision to participate in a study or not. The process of

consent is more than the mere participants' signature. It should be understood as a continuous process from the beginning to the end of his/her participation in research.

Important elements of consent include information, comprehension and voluntariness. Researchers should ensure that potential participants have understood the information provided, clarify anything that was unclear, and should judge whether an assessment of capacity to consent is needed and if so, carry it out.

In the context of technology and older people, in addition to this, other relevant themes within the principle of autonomy include empowerment, control and self-determination (Schicktanz and Schweda, 2021; Keenan et al., 2021).

Beneficence and maleficence

The concepts of beneficence and of non-maleficence are related to participants not being harmed through the conduct of the study. This involves trying to do what is best for someone and avoiding doing something that might cause them harm. The principle of beneficence involves not just that the research should do no harm, but that it should promote participants' wellbeing. The principle of beneficence is behind efforts by researchers to minimize risks to participants and maximize benefits to participants and society.

Justice

The principle of justice is complex and deals with the concepts of fairness, equality and equitable treatment. This principle requires that researchers are always fair to the participants and that participants' needs should always come before the objectives of the study. Researchers should carefully think about who benefits from research and who bears the risks of research. It can also relate to the selection and inclusion of participants in the study, i.e. that participants should be selected for reasons directly related to the problem being studied and not "simply because of their easy availability, their compromised position, or their manipulability". This includes issues around the potential exclusion of people who are marginalised. For example, not involving, or making it difficult to involve, any patient group in clinical research could be described unjust.

This principle also ensures that the questions addressed in the study are of relevance to the communities participating in the study.

3.2 Risk of cognitive decline and dementia

The population of Europe is growing older. In 2020, more than one fifth of the population in the European Union was aged 65 or over (EuroStat, 2020). Life expectancy is also increasing, rising an average of 77.7 years for someone born in 2002, to 81.3 years for someone born in 2019 (Alzheimer Europe website). Although these are both facts to celebrate, as the primary risk factor for dementia is age, the continued increase in life expectancy and population ageing also increases the likelihood of people developing the condition.

Estimates suggest that, currently, near 8 million people are living with dementia in the European Union and this figure is expected to continue to increase. Dementia is a major cause of disability and dependency and impacts the lives of the person diagnosed with the disease and the people surrounding him/her (WHO, 2019). It is one of the most feared diseases of ageing. Despite several efforts, to date dementia remains a non-curable disease and in Europe and there is no disease-modifiable treatment available for people affected.

Over the last few decades, the field has moved to what is now framed as the earlier stages of the disease. Alzheimer's disease is now conceptualized as a continuum including dementia and the pre-dementia stages of the disease. This includes people with biomarkers (amyloid, tau) and no symptoms, people with biomarkers and some cognitive impairment and people with biomarkers at the different stages of dementia (mild, moderate and severe dementia). It is generally believed that interventions to delay onset or stop progression would be much more beneficial if initiated before the onset of dementia.

A great amount of research has also focused on dementia prevention. Currently, our knowledge of the risk factors (modifiable and non-modifiable) and the potential prevention of cognitive decline and dementia has significantly improved (Livingston et al., 2020). We have good evidence, for example, of how risk factors in early life (education), midlife (hypertension, obesity, hearing loss, traumatic brain injury, and alcohol misuse) and later life (smoking, depression, physical inactivity, social isolation, diabetes, and air pollution) can all contribute to increased dementia risk (Livingston et al., 2020). According to this, it has been estimated that up to 40% of dementia cases could be prevented or delayed by targeting these risk factors throughout life (Livingston et al., 2020). The WHO Global Action Plan (2017-2025) included dementia risk as one of the Plan's action areas and concludes that "reducing the level of exposure of individuals and populations to these potentially modifiable risk factors, beginning in childhood and extending throughout life, can strengthen the capacity of individuals and populations to make healthier choices and follow lifestyle patterns that foster good health".

However, risk is a complex concept which can be very difficult for the person to fully comprehend and for the clinician to communicate (Visser et al., 2021). Risk can be defined as "the likelihood, or in statistical language probability, of an individual in a defined population developing a disease or other adverse health problem" (Bhopal, 2016). Being at risk or at higher risk of a disease does not mean that the person will certainly develop the disease or, perhaps, not in his/her lifetime. The definition of risk, therefore implies, by definition "uncertainty" (Visser et al., 2021).

There is considerable interest from members of the public to know about their risk of developing dementia in the future (Alzheimer Europe, 2011). It also been argued that knowing about their risk of developing dementia could help people to get a more timely and earlier diagnosis of dementia and prepare for the future (Visser et al., 2021). Other positive aspects of the communication and management of risk, include the right to know of individuals as well as the possibility to act and do something about managing or event reducing such risk. This possibility to act has been sometimes criticised in the absence of approved disease-modifying drugs, however, many researchers highlight the potential benefit of changes in lifestyle which are well-known modifiable risk factors in dementia. Many risk factors for cognitive decline and dementia are quite similar to those for other conditions such as vascular conditions. Engaging in behaviours and changes (e.g. exercising, healthy diet, etc.) for brain health, can also bring other positive health outcomes for general or vascular health.

But regardless of the many and undeniable benefits of risk reduction and brain health, communicating risk to a person who is and feel otherwise healthy also raises several concerns. Examples include the potential negative impact on wellbeing as it may cause distress, depression, anxiety or may even change the perceptions of oneself and others (Milne et al., 2018). Stites and colleagues also warned that "emerging evidence from people diagnosed with MCI and research volunteers in Alzheimer's disease prevention trials suggests that stigma currently associated only with the dementia disease stage may spill over to individuals with only mild or even no symptoms. In other words, cognitively unimpaired persons identified in a

"preclinical" stage of the disease based on biomarker results may experience stigma, such as social isolation, discrimination, and internalized distress." (Stites et al., 2018).

The increasing interest in prevention, risk reduction and brain health has increased the number of interventions and campaigns to raise awareness of this topic and promote healthier lifestyles among the population. Horstkötter and colleagues (2021) reflecting on a campaign for dementia risk reduction conducted in the Netherlands, raised some ethical issues such as the emphasis some of these messages have on the person. In their opinion, "the emphasis on "I" could also trigger undue responsibilisation and blaming the victim, as if one is personally responsible for either or not developing dementia" and lead to a situation in which people with dementia get the impression "that it was their own fault" they contracted the condition. They highlighted the complexities of finding the right messages to convey to, on the one hand, promote these positive messages about prevention and risk reduction, whilst, at the same time, not risking blaming the person (Horstkötter et al., 2021).

Similar critiques are also found in the area of the more broader concept of health ageing, as some scholars have suggested by "focusing the responsibility on individuals to maintain physical and cognitive function, the successful aging paradigm reflects and serves efforts to limit the state's responsibility to provide social and other supports for elders and people with disabilities and, notably, to address the social and structural inequities that create illness and disability in the first place". In this line, it is important to also bear in mind that many modifiable health-related behaviours such as smoking, excessive alcohol consumption, poor diet, and lack of physical activity tend to cluster around inequalities (Kino et al., 2017) which may occur particularly in Black, Asian, and minority ethnic groups and in vulnerable population (Livingston et al., 2020). Wallace and Brayne (2022) also highlight the relevance and benefits of broader population-based approaches (instead of individualised approaches to risk reduction) as these are likely to be the most impactful, cost-effective, and meaningful ways to reduce the global burden of dementia and can address inequality (e.g. instead of counselling individuals on healthy eating, developing policies that improve access to adequate nutrition).

Others (Lawless et al., 2017, as cited in Horstkötter et al., 2021) have also argued that messages and interventions to reduce risk should balance the benefits and burden, as for example, the possible benefits that eating healthier or doing exercise can bring to the brain when growing old and the possible burden of having to engage in these behaviours for very long time. They also argue that messages around brain health could empower people and contribute to their feelings of sense of self-efficacy and control; but it could also put social pressure on people to engage in certain behaviors supported by science and not decide in favour of other lifestyles or priorities in life. They further argued that people who eventually develop dementia may be further stigmatized or blamed as it could be understood as if they had behaved irresponsibly while still being young and healthy.

The manner in which this is portrayed is equally important, in the case of healthy ageing for example, media portrayals of successful ageing involve often white, middle class, free of disease and disability older people and the images and expectations may not be in line with those of the population, and do not reflect the diversity of older people, many of them who may live with different health or living conditions (e.g. other diseases which may affect what they can eat or how active they are; pension; previous life, interests and hobbies or lack of them, etc.).

It is also important to consider that no everyone at risk will eventually develop dementia. The concept of a higher risk in Alzheimer's disease is quite broad and includes many different situations including people with and without any clinical symptoms (e.g. with and without cognitive impairment). Even in the case of people

who are experiencing cognitive problems, the progression from Mild Cognitive Impairment (MCI) to dementia does not necessarily always happens (Gomersall et al., 2015). The range of reported annual rate of progression of MCI to dementia in the literature is very wide, ranging from only 5% to 39% (Thaipisuttikul et al., 2022). The amnestic subtype of mild cognitive impairment (aMCI) is associated with an increased risk of developing Alzheimer's dementia, corresponding to an annual conversion rate of 30% (Ottoy et al., 2019). However, it is also important to bear in mind that 16% of people with MCI may revert to normal cognition after 1 year (McGirr et al., 2022).

Communicating and managing risk is not only a challenge for the lay public but also for the clinicians and researchers. They should ensure that the person understands the condition, the magnitude of their risk and the implications of such risk for them (Visser et al., 2021). The expected timeframe for developing cognitive deterioration or dementia is also a very important factor. For example, Horstkötter and colleagues reflect about what might it mean to the personal identity of healthy people "if they are advised to care about preventing a disease that is still far away and for which health benefits, if any, will become visible only decades from now?".

The discussions about risk reduction are often also linked to people with a genetic predisposition or who already have some of the biomarkers of Alzheimer's disease (amyloid, tau) as they may have an even higher risk of developing dementia. However, receiving a positive predictive test result, and disclosing it raise several ethical challenges and concerns, mostly because of the unclear predictive value and the possible consequences (Alpinar-Sencan and Schicktanz, 2020). These challenges and ethical concerns could be classified into three categories; the clinical, the personal and the societal (van der Schaar et al., 2022). Firstly, the clinical validity and utility of screening tests are not clear. The clinical validity is also questionable because current screening tests are based on the identification of abnormal levels of amyloid-β and tau. Although these two biomarkers may improve the accuracy of the diagnosis, cognitively healthy individuals with abnormal levels of these proteins do not necessarily develop dementia (Livingston et al, 2020). Besides the clinical context, some personal considerations should be considered when deciding on the disclosure of the results of a screening test. Knowing an abnormal biomarker result can provide both certainty and uncertainty. Risk disclosure can allow the person to prepare for the future and take part in prevention trials. Uncertainty may arise because of the lack of clarity of the information provided by clinicians (Gomersall et al., 2015). The personal context also relates to the right to know or not to know the test results, which has to be respected as well, since the individuals' wishes should be the ones determining the disclosure decision (Ursin et al., 2021). Although the willingness to learn about their biomarker test results enhances the ability of the individuals to act on that clinical information (Milne et al., 2018) a positive screening test may also lead to discrimination, stigma and social status changes (Milne, 2010).

The concept of risk and its communication is challenging. Regardless of the benefits and challenges of disclosing the likelihood of having dementia in the future, it is essential that clear and sufficient information is provided to the person. This will allow them to fully understand their risk and prognosis so they can plan their future, take part in clinical trials and use digital technologies to support them if they wish to do so. However, this is as important as respecting patients' autonomy and their refusal to take a genetic/biomarker screening test and/or not-knowing the results of such tests or of their risk. Risk communication is based on shared decision-making that cannot happen when people do not have accurate information about the research, methods used in research and the potential risks and consequences (Visser et al., 2021).

3.3 Use of technology by older adults

There has been an increase in the use of technology (especially smartphones) and internet across all age groups over the last decade. Thanks to the connectivity to internet, smartphones can facilitate access to many different activities such as playing games, listening to music and socialising (Busch et al., 2021). The recent COVID-19 pandemic may have also an impact on the use and attitudes towards technology for different activities.

However, there is a great diversity in the way older people use and perceive technology and internet. Hanninen and colleagues (2021) describe a continuum of digital technology use among older adults ranging from active and independent to more limited use. In addition, geographical differences also exist in access to technology and internet. Data published by EUROSTART for the use and access to internet during the pandemic in 2020, showed that although a very large proportion of people aged between 65-74 in Denmark, Luxembourg, Sweden and Finland (94%, 91%, 91% and 88% respectively) had used internet in the last 3 months, in other countries such as Bulgaria, Croatia and Greece, this was much less frequent (25%, 28% and 33% respectively).

Therefore, while access to technology and internet has become widespread, there is still a digital divide, with many older adults still facing significant barriers to accessing them (Gallistl et al., 2020). Some experts (Negreiro 2015 as cited in Gallistl et al., 2020) have suggested that while the first level of digital divide (i.e. inequalities in access) may have been reduced, the second and third level (i.e. inequalities in competence and performance) are still prevalent. Digital inclusion should include access, skills and attitudes towards technology and internet.

Some of the identified factors that can have an impact in the digital inclusion of older adults are: psychological factors (e.g. higher computer anxiety, negative attitudes, concerns about security issues etc); health-related barriers (e.g. poor eyesight) and socioeconomic factors (e.g. education and income), as well as the fact that some products are poorly designed and not suitable for older adults or the instructions to use them are not appropriate (e.g. in small font or using unfamiliar vocabulary which does not help to understand the instructions) (Gallists et al., 2020, Wang et al., 2019). It has been also pointed out that some technologies or devices specifically developed for older adults may encompass a "stigmatizing symbolism" that could prevent them from adopting these technologies and that some people may fear that the use of technology would replace human contact (Wu et al., 2015; Wangmo et al., 2019).

On the other hand, older adults' confidence in their ability to access and understand technology ("perceived usability"), the perceived benefits or advantages of using it ("perceived efficaciousness") and perceived collateral damages ("unintended harm") can all play a positive role in motivating them to use and engage with technology (Wang et al., 2019, Golant 2017).

It is important to also bear in mind that there is a great heterogeneity among non-internet users. Some literature suggests that the more relevant factors affecting the digital divide are not linked to age but to low education and level of experience with digital technologies. The attitudes and openness towards new technologies and use of internet can also play a very important role (Gallistl et al., 2020), highlighting the relevance of people's specific tastes orientation and attitudes in later life. Gallistl and colleagues (2020) therefore suggest that to promote the use of technology and internet among older adults, it should be designed to "fit in with the lives of older people".

In addition, it is important to consider that whilst some older people may not be able to access technology or internet for different reasons, others may simple not want to use digital technologies in later life. Learning new ICT skills can help to improve digital independence. However, as suggested by Hanninen and colleagues (2020), the development of skills does not guarantee a linear progression, as the person may not be proficient in all aspects of technology at the same time or the person and/or the technology may change (e.g. due to age-related impairments or illness or to changes in the technology rendering it more complex).

Another important type of technology in our current society are ubiquitous technologies (e.g. like fitness tracking devices) which have spread rapidly (Fietkiewicz et al., 2020). The use of tracking devices can bring multiple benefits for the user but they also arise concerns such as feeling dependent or surveyed and concerns regarding privacy and security of the data collected by the devices (Fietkiewicz et al., 2020). Some of the concerns raised in the literature in relation to these tracking devices are related to privacy protection, third-party access to data, access to personal information by apps, lack of feedback from data collected by digital devices or researchers, and the overall feeling that "once the information is shared, it is ultimately out of their control" (Fietkiewicz et al., 2020; Wang et al., 2019). There are different perceptions of data sensitivity and privacy concerns. Overall, users of these devices (both current and previous users) have different views on what they would define as sensitive data and fewer concerns than non-users. However, there are certain categories such as GPS use, email and contacts that tend to be perceived as sensitive by all regardless of their use and familiarity with the device.

3.4 The Lethe study

The Lethe study is based on an existing, well-known multi-modal intervention for dementia risk reduction: FINGER, "Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability". FINGER has looked at the effect of a lifestyle programme (multidomain intervention) in delaying cognitive decline in older adults who have some risk factors. The FINGER study was conducted in Finland, between 2009 and 2011, and included 1,260 participants between 60- and 77-years of age. Participants were selected using the CAIDE Dementia Risk Score (including age, sex, education, hypertension, hypercholesterolemia, obesity, and physical inactivity) (Solomon et al., 2021). These participants were divided in two groups; i.e. the "active" and the "control" group:

1. The participants in the active group followed the FINGER intervention led by professionals for two years. This included group and individual sessions in the following areas:
    - Nutritional guidance. A diet rich in fruits, vegetables, whole grains, fibre-rich products, rapeseed oil, and fish, and with a limited consumption of saturated (hard) fat, refined sugar and alcohol.
    - Physical exercise. The exercise program included:
        - muscle (strength) and balance training in the gym two to three times per week.
        - aerobic training (e.g. walking, jogging, aqua gym) several times per week.
    - Cognitive training included a computer program to exercise memory, mental speed and executive function (i.e. planning and organizing). Participants did two to three sessions per week each lasting 10 to 15 minutes.
    - Monitoring of Cardiovascular health: participants met regularly with a study nurse and physician to measure their weight and blood pressure, discuss lab results (e.g. blood tests), and get extra motivation for the lifestyle changes.

2. The participants in the control group did not follow the FINGER programme, they received basic health advice.

After the two-year study, researchers found that the participants who received the FINGER intervention performed better in cognitive tests than those who received basic health advice. Their risk of cognitive decline was also lower.

Lethe is building on the FINGER intervention. It will help to understand how some parts of the FINGER intervention could be implemented or measured using existing technology (e.g. apps and wearables such as smart watches, smart glasses etc.).

The Lethe study is a feasibility study and will test a hybrid version of the FINGER intervention using technology. It also incorporates some novel aspects such as monitoring sleep and the use of meditation/relaxation which were not included in the original FINGER study. The study will be conducted in Austria, Italy, Sweden and Finland and will last 2 years. As FINGER, the Lethe study will involve older adults (60 to 77 years old) with no cognitive impairment. The Lethe study will use a hybrid approach as some aspects of the intervention will be delivered and monitored face to face, whereas others will be digital. Some of the technology and apps used are commercially available tools (e.g. Fitbit) whilst some apps and surveys will be developed specifically for the study. Participants will receive the Fitbit from the research team and offered a research smart phone if they prefer to use this instead of their own personal phone. Further details of the study can be found in Deliverable 7.1 (study protocol).

The concepts of risk reduction and the use of technology by older adults are therefore key elements of the Lethe study. The principles of autonomy, beneficence, maleficence and social justice are taken as the conceptual framework to consider the ethical and social implications of the study. These are important principles for the Lethe study in many different aspects. For example, some of the participants may find out about their risk of cognitive deterioration as a result of their participation in the study. This may have very important implications for how themselves and others perceive them and for their future (i.e. for those who already feel they are at a higher risk because they had relative who had dementia). They may also have fears and concerns about developing dementia in the future, and therefore have expectations about how the intervention could delay this or, conversely, they may feel a lot of pressure and not feel prepared to make the necessary adjustment or changes in their lifestyle or may not have the means or necessary support. In addition, the digital aspects of Lethe may also bring several other challenges linked to these principles. Technology can significantly help and support older adults but also as can cause stress or discomfort, or simply put off some people who would have been otherwise interested in this type of programmes. The Lethe study is therefore very relevant and its findings may be very beneficial for a population which is growing older, where fewer resources are available and after the COVID pandemic, where we learned about the difficulties of continuing with a healthy life during confinement and social isolation. However, this approach also raises ethical and social issues that must be addressed.

4 Approach

Alzheimer Europe, in close collaboration with the Lethe partners is leading the Public Involvement activities of the project. This included setting up a project-specific Advisory Board (AB) composed of people from the general public who are interested in the topics addressed in the project and who are at a higher risk of cognitive decline. The four clinical partners involved in the Lethe project (KI, THL, UPG, MUW) identified 1-2 people at risk who were interested in joining the AB. The Lethe AB is currently composed of 7 members (2 from Italy, 2 from Sweden, 2 from Austria and 1 from Finland). One of the members has mild Alzheimer's dementia and the others are at higher risk.

In addition to this project-specific AB, the project has strong links with another similar project also based in the FINGER intervention (the JPND funded project, EU-FINGERS https://eufingers.com/). The Lethe project is building on some of the relevant discussions around the FINGER intervention already addressed by this AB. Members of these two AB have participated in joint information workshops and will be working together in some areas of interest for both projects.

The EU-FINGERS AB is composed of 15 members of the public, including people who have participated in the FINGER intervention, people with Subjective Cognitive Decline, Mild Cognitive Impairment, people with dementia and carers. Further information about this AB can be found: https://eufingers.com/for-general-public/patient-and-public-involvement/the-advisory-board/

The meetings of these ABs are planned and organised by AE in close collaboration with project partners. In addition, members of KI and of THL have been actively involved in co-facilitating the discussions of the ABs. Background materials, in lay terms, about the topic to be discussed in the meeting are prepared and send to members of the AB, 10 days in advance of the meeting. The meetings and materials are in English but if necessary, members of the local clinical team can provide support for translations to members while preparing or during the meetings.

The Lethe AB was set up in October 2021 and has, so far, held three meetings. Meetings lasted between one and a half and two hours and were held online. One of the meetings was specifically on the topic of ethical and social implications of the project (see background materials and questions sent to the AB in Appendix 1). The other two meetings, while not specific on the topic of ethics, addressed issues related to the protocol and use of the technology by older people which are relevant for this report.

The EU-FINGERS AB was set up in February 2020 and has held 6 meetings. Some of these meetings were related to the relevance of dementia prevention, terminology used and different aspects of the EU-FINGERS master protocol.

The information provided in section 5 of this report is based on the feedback provided at these various meetings by these ABs. Parts in the text which are in *italics* are comments made by members of the AB. All the rest of the text in Section 5 are summaries of the discussions with members of the ABs.

Some of the main issues, relevant to the ethical and social implications of the study, addressed at the different meetings include:

- Issues related to terminology and how to communicate about the topic
- Issues related to the use of technology by older people
- Issues related to date privacy, data sharing and confidentiality

- Issues related to beneficence and promoting wellbeing
- Issues related to stigma, diversity and inclusion
- Issues related to autonomy: information and consent

These meetings and activities are within the framework of Public Involvement (i.e. are not qualitative research). The opinions of the members of the ABs reflect opinions, concerns and suggestions from the perspective of members of the public, but these are not generalisable or representative of any population. These views and suggestions can greatly help the research team in understanding how some of the participants may feel, anticipate challenges and plan for solutions and tools which can support the participants during the study. Their feedback was used to build the recommendations included in this report.

5 Feedback provided by the Advisory Boards

All the information included in this section are summaries of the discussions with the members of the Advisory Board. The text in italics are direct quotes or statements made by members.

5.1.1 Relevance of the topic and issues related to terminology and communicating about risk

Members of the Advisory Board felt that the topics of brain health and risk reduction are very relevant, particularly for people affected or with an interest in dementia. However, overall, these topics are not given as much importance by society. It was discussed that although brain health, prevention of dementia and risk reduction are very important topics and should be a priority, "*actions do not always reflect this and not enough is being done to address these issues"*. There were also discussions about differences in information in different parts of Europe. In countries, like for example Finland, there has been a lot of awareness raising around dementia and brain health and there is now quite a lot of information publicly available. However, this is not the case in other countries where there is not enough information available and or is not a priority in the country.

In terms of the terminology, members of the Advisory Board felt that the terms "prevention of dementia", "brain health" and "risk reduction" are terms which most people may be familiar with. The three terms (i.e. "prevention of dementia", "brain health" and "risk reduction") share some similarities and somehow overlap, "*they all together bring something to the same table*". However, these terms do not mean the same and can bring different things to mind (including feelings and emotions) and therefore, they should not be used interchangeably.

Prevention of dementia

This term is still very often perceived negatively and some people may not feel comfortable with it, as in some countries, there is still stigma associated with the term "dementia". The word dementia still "*evokes fear and other negative feelings"*. However, this might not be the case in all countries in Europe as in some countries like Finland, there has been a lot of awareness raising work.

Another issue is that some people may understand "prevention" as that it is possible to ensure that they will never develop dementia or that it is possible to cure it, however, this is not something that it is realistic or achievable. As one participant explained: "*It is not a good term. Can dementia really be prevented?".*

On the other hand, prevention is a word which can prompt people to act and find solutions. In this case, prevention can be perceived as a positive term linked to "*taking meaningful actions*" and "*coming up with solutions to problems*". Examples of this included acting wisely, taking care of yourself, leading an overall healthy life and having a healthy lifestyle and habits.

Brain health

Brain health was described as a broad overarching term, "*An umbrella term with many terms underneath it"* and as *"positive and appropriate*" as it focusses on health rather than on the disease. A positive aspect is that this term can be applied to a broad range of people and to different conditions (i.e. not just dementia). It could apply to every person even if they never develop dementia and should be considered from a life-course perspective (e.g. "*taking care of the brain should start from the time the person is born"*).

Some members emphasised that when communicating about dementia or cognitive decline the message should be positive and the messages should focus on health rather than on the disease: *"it is important to encourage people to maintain their brain health, rather than protect themselves against a negative outcome".*

On the other hand, it was argued that this term, while positive, lacks the precision and clarity that other terms such as prevention or risk reduction have, and it was felt that it is "*hard to give an exact definition of the term*".

Finally, although brain health is a positive term, in some countries this is not a topic people feel comfortable discussing with others openly or a common topic of conversation.

Risk reduction

Risk reduction and prevention of dementia are terms which are connected, and both can imply that the person "*takes action*". Risk reduction was described as "*having a lifestyle which reduces the risk factors for developing dementia", "living in a way that helps prevent the disease*", *"taking concrete actions*". It was perceived as related to the early stages of the disease, either when people are worried about developing dementia or if they have experienced early symptoms.

Some members felt this was a positive term as it reflects that there is something that can be done to reduce risk. However, "risk" can be a difficult concept to grasp. For example, when referring to risk reduction it should be clear that certain risks cannot be modified (e.g. age, genetics) and it should be emphasised which are the modifiable risk factors.

Preferences on terminology use

The three terms - "prevention of dementia", "brain health" and "risk reduction" - could be appropriate and the use may be dependent on the context and goals.

The term "brain health" conveys a more positive message and does not focus on disease, fear or negative outcomes.

Some members felt that overall term prevention should be avoided as it is "*too aspirational*", whereas risk reduction is something more accurate and that can be achieved.

It was also mentioned that regardless of the term used, the person should receive clear and appropriate support and information and about what it means. With the appropriate context and support, either of the terms could be acceptable, however many felt that they would still feel concerned when using these terms (terms directly linked to dementia) or talking with friends and relatives.

Conclusions

- Brain health is a positive, non-threatening term as it focusses on health rather than on disease and it is applicable to a wide range of people. It is a term that is also relevant once the person has a diagnosis of dementia.
- Prevention of dementia and risk reduction are more specific terms and may be more likely to prompt people to act, e.g. take concrete actions or find solutions.

- All terms may be appropriate when used in a safe context (e.g. when discussing this with the researcher or doctor, if they provide the necessary information/support) but could also worry or distress people if used in a not appropriate context.
- There is still stigma in some countries, and even in countries where stigma is no longer an issue, people do not discuss openly with others about their brain health.

5.1.2 The use of technology in the study

Members of the Advisory Boards consulted were familiar and used technology in their daily lives including apps and reminders that they set themselves using their alarms. In general, the most popular apps were those for communication and social purposes (WhatsApp, Zoom). They liked these apps as they connect them to people who are important to them (e.g. grandson, siblings etc.), are easy to use and what they offer is meaningful and relevant to them.

However, the use of technology can be also be challenging or may put some people off participating in a study. Some people do not like to use technology or using it too much. They may prefer personal contact with other people.

- *I like spending time with my friends and doing other things that are not related to technology or to my phone.*
- *I have tried to use a GPS and it didn't work. I prefer to ask someone if I need to.*

In addition, apps and devices for health can be less well known/used by older people. Some people may be open to exploring them, particularly if they are concerned about their brain health and feel this could help.

Different users may also have different preferences and perceptions about the time and intensity they would like to spend using technology or apps. For example, some may not like feeling dependent on their phone, having to dedicate too much time using technology and may prefer to spend time socializing with friends or enjoying their hobbies.

- *I have tried to select some apps (sleep, activity, diet) to use, but it demanded a lot of my personal time so I gave up.*

It was also discussed that the use of technology could also have a negative impact on wellbeing as it can add stress to people's life, particularly if it is too complicated or the participants do not understand how it works. Technology and apps should help people, not add extra work. What it is asked to do should not be too much or interfere with other activities they like to do.

Members of the AB consulted were quite open to new apps and devices. However, it was emphasized that the apps/devices should be helpful, meaningful, and relevant to the participant, and that the study should not introduce several apps just because they exist or are "trendy", but everything must have a clear purpose and added value.

In addition, the technology used would need to adapt to their lives and "*go along with them*" (e.g. adapt to future needs). In the case of some less frequently used technology (e.g. robots), the relational aspect and its presence at home was very important. It should be a nice, easy-to-use, friendly and helpful presence. Some people may be reluctant and need time to get used to the new technology.

People who know or think they are at a higher risk of developing dementia may be already trying to change aspects of their lifestyle (being more active, eating healthier, using some existing apps etc.). It would be

important to consider how to include the Lethe intervention with these already existing changes or strategies.

Conclusions

Technology is part of the daily life of many people regardless of their age. It can bring many benefits and many people particularly appreciate the social aspects and feeling connected to other people. However, not every person is familiar, has access, likes or feel comfortable using technology and internet. Some people may feel using technology is demanding, takes up too much of their time, can be invasive or may replace their personal contact with other people. Some people who are worried about their brain health or experiencing memory problems may be already using some other apps, devices or strategies which are working well for them. Technology, if not appropriately designed, can have a negative impact on people's wellbeing. Some forms of technology can be perceived as invasive and it is important that technology fits and adapts to people's lives and preferences.

5.1.3 Data sharing, data privacy and confidentiality

Privacy and confidentiality are very important to people, particularly if they are sharing data about their lives and their health over a long period of time. Aspects that may be important for the participants may include that the data is anonymised and that is used for the purpose of the study and not misused. Participants' concerns may also be related to their perceptions of the nature and sensitivity of the data collected.

Data sharing is becoming a part of our daily lives. Many people are sharing their data, even sometimes without noticing (e.g. in social media, when buying something online or with the supermarket's card). People have different understandings, attitudes and experiences of data sharing and privacy. Some possible participants may have no questions or issues in relation to how their data is handled, stored and used, whilst others may feel very strongly about this. Recent stories in the media about the use and abuse of data sharing may also have an impact on this and some people may therefore feel more worried and protective of their data.

- *No, they have concerns too because we are always sceptical about what we are testing. We are using it all the time. I don't think it in that way.*
- *First of all, I am not sure that… ok, we have to reassure the participants but we all are really easy-going about this subject apart from that sometimes we are a little bit paranoid about our data so maybe what is important is to inform the participants as clearly as possible,*

Another relevant aspect to consider is the complexity of the information regarding how the data will be collected and used in the Lethe study (e.g. Fitbit data will be collected by the company, the RADAR base system and the project system).

- *It's not easy at all, because there are so many issues, ethical, legal…. I discovered that there are privacy limitations… so, it is a very complex matter.*

To ensure that all issues linked to how the data is collected, stored and used are clear all the information should be in the mother tongue of the participant (i.e. Fitbit-related policies). Lack of clarity about this or misinformation may result in people deciding not to participate or in people not making a real informed decision about their participation. In addition, the contents of any policy related to privacy and data sharing

should be clear, accessible and in a tone, which is appropriate. In addition to this, it should also be clear to the person the consequences of the policy and what it means for them.

- *I am particularly stressed because in our document it is written that sometimes is not possible to have policies written in other language than English. If this is the case, I think is very important that every country has these written in their native language. I have seen these issues in many cases, so I think I have an idea about it, so we have to share these important…to avoid people being scared so they will not participate because of prejudices.*
- *It should be in a simple and easy language, no matter in which language it is. Very simple and very clear.*
- *I am quite good at reading in English, but for me is not about the language, it is about the meaning of it. But I know the information that is there. But what does it mean, what does this mean for me?*

Participants also felt problematic that these policies and documents are often written from a legal point of view and may not be adequate for lay people

- *I think this is ok, but then I went to these links and there is a lot text in the links, I don't like to read. It is too much. I understand legally these texts are very important and they should include everything. But at this point a summary of this text would be very helpful. If you want to read, just read it, but… well, I think you understand me.*
- *Of course, there are the legal points, so the responsible or the research want to be sure that from the legal point of view everything is fine. But then there is an ethical point and we want to be sure that the person that will participate will also trust. In my opinion this sounds too legal, so it is like, Ok we made it and we give you the information, and you sign it and so we are quite safe. But I would like more concern, people should try to make the information not as a company … we want the essential points to be clearly understood.*

Another important topic which was addressed several times was trust. It was felt that in order to participate there should be some degree of trust from the participant in the researchers. Participants may trust research more when is led by organisations with a good reputation and experience in research. However, it was also felt that participants should not just have "*blind trust*" and that informed consent involves that every participant clearly understands what their participation involves. There should be a good balance between the trust of the participant in the research team and the information received. Transparency and honest and clear communication could help to build this trust.

- *There are so many issues but you have to trust. I think one of the most important things here is not to have too many concerns. I have to trust you because I couldn't work with you otherwise.*
- *People who are joining, they trust. When they join, they have to trust. If I am joining and they say that your information is only for the research, and not to sell, I have to trust. If I don't trust, I am not joining.*
- *But the important thing is not just to trust; the important thing is the consent. People should be very well informed. I don't like blind trust very much.*
- *It is important to have the privacy policy in my native language, because it is a very complex thing, and of course, you must trust and not to be scared if you take part of these projects. And to understand the privacy policy is important. All the information should be very clear and in their mother tongue.*

An example of how people may tend to trust the researchers was related to the conversation of whether they felt participants should be offered to use their own Google account for using Fitbit or a "dummy" account created by the research team for each participant. All members of the Advisory Board would prefer the dummy account, as they would feel more confident and trust more an account created by the researchers than their personal ones.

- *I have to say that I don't understand that much, so it is difficult to say. I am used to trust. (…) I don't understand techniques. So, I would trust that your account is better.*
- *I prefer the second option, your google account, because it will be more… safe in a way. I don't know exactly what that means, because I am rather good at technology. (…)*
- *Your account, because I think makes things simpler and easier.*

Conclusions

Privacy and confidentiality are very important but people experience these terms in different ways and may have different attitudes toward them. Information about data collection, storage and use may be quite complex and often explained in legal terms. Information and trust are very important. For many participants, participation may be indeed mainly *a question of trust*. However, every participant should be adequately informed to make this decision. Also, to ensure that less trusting people are not discouraged from participation in the study.

5.1.4 Wellbeing of participants

The principle of beneficence states that the research process should ensure that "persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their wellbeing". In the Lethe study, this could be related to different aspects of the study:

- The difference between the active and non-active intervention and how each could impact on participants
- The provision of support as the intervention was considered as quite demanding
- The wellbeing of participants after the end of the study and related intervention

Active and non-active group

The intervention was described as holistic, comprehensive and including "*everything that is needed*". It can give participants structure and clear indication/instructions on what to do to decrease risk. Regular checkups with healthcare professionals and close monitoring of progression were also perceived as a possible benefit for participants in the active intervention. However, there were also concerns. Whilst interesting, some participants may perceive the intervention as overwhelming and feel it is too much "pressure" on them to make the changes that are part of the intervention. In addition, some older people may have co-morbidities (e.g. cancer) or other conditions which may complicate or prevent them from making changes in some of the domains as required (for example exercising) and may feel bad about this. Also, whilst the ongoing monitoring was perceived as positive, some people may feel like someone is constantly watching them ("big brother") and perceive this as more invasive.

In relation to the non-active intervention, some members felt participants might feel disappointed or dislike not being allocated to the active group. This may be more relevant for people who think they are at higher

risk or are experiencing some memory problems and may see this as a missed opportunity for them to do as much as possible.

On the other hand, some members felt very positive about the non-active group and for them joining this group would also be very beneficial. In this case, members felt this would be a way to make changes in a more flexible manner and at their own pace (as opposed to the active group which was perceived as more demanding and stressful).

Some members suggested that the self-guided intervention could be complemented with some elements of the active group (e.g. access to cTrain but on their own; no scheduled sessions but independent training). Also, to support motivation and adherence to lifestyle changes, the self-guided intervention should include evidence-based information about lifestyle changes for dementia risk reduction. It was also mentioned that people who are already motivated, have some information and perhaps are already making some changes to improve their lifestyle are more likely to adhere better to the study.

- *Providing evidence-based information about lifestyle changes for dementia risk reduction will be very important at the time of recruitment (evidence of the relevance and impact of the intervention). It is also important to clarify and manage expectations (e.g. what risk reduction means, how long it takes to reduce risk, etc.)*

Some members of the ABs were concerned about the participants' expectations when joining the study, and suggested that the amount of detail and how both interventions would be presented to the participants before they had been allocated to the interventions were very relevant. It was also very important that participants had a clear understanding of risk and reasonable expectations about the benefits of risk reduction and the length of time and effort required for the intervention to make an impact on their risk.

Provision of support

Participating in this type of interventions can be quite demanding for participants, and therefore some members of the ABs felt that support would be critical. Different types and sources of support were mentioned including support from the researchers, from "peers" (other participants) and from their own families or friends. It was also highlighted that external support provided as part of the intervention would be relevant and would help the participant not to rely too much on his/her family. This could promote the autonomy of the participants. Support from the research team was also expected after the study finished as the lifestyle changes are beyond the study and part of the life of the person.

- *I would like to have the support that allow me to not weigh too much on my family, my son is a doctor and I do not want to be her patient I want to be the grandmother of his children. (…)*

The provision of support is crucial to promote the wellbeing of participants. This should be provided in an appropriate and personalised manner which corresponds to the person's needs and preferences.

- *It is important to keep in mind that we are all unique, support needs to be personalized and intervention programs need to be tailored.*
- *I got very excited when you mentioned digital tools, there are these live cooking classes for example. But it's important that one is able to contact someone if needed (e.g., if there are any questions), participant is updated regularly about the progress and feedback is provided.*
- *I'm a very social person, having contact with real people is important. Technology can be difficult for people with cognitive problems.*

End of the study

There were some concerns about the end of the study and intervention. It was perceived as the researchers' duty to provide some form of support and not to "leave anyone behind" once it ended. Some participants may be able to continue on their own but others may not have the motivation or resources to carry on. Information about the results and conclusions of the study to the participants could also help participants and motivate them.

- *I think participants should be supported somehow later on. Don't leave them alone.*
- *To continue with the life style changes it pretty much depends on whether the person receives support. If not, the exercise will stop. A social worker can see the participant regularly to encourage him to do the exercises. Otherwise, I think the exercise will stop.*
- *I need to go on by myself now that the study is finished, but it would be great to also have some sort of support afterwards.*
- *The programme should not finish completely with the study. It is good to have a point of reference from the study team that continues afterwards, someone to whom I do not have to explains all the details etc. (like to the GP) and having regular meeting to exchange views and experiences.*
- *It is important that the researchers inform about the trial results, whether the intervention was successful or not, what were the main findings etc. Push the positive aspects and encourage participants to continue if beneficial effects were observed. Disclose the results even if there were no significant findings.*

Conclusion

Interventions to reduce risk of cognitive decline, such as Lethe are very relevant. Participants may greatly benefit from an intervention like Lethe as it can give specific advice on how to act and a supportive environment to carry out these changes. However, issues to consider are the expectations that participants may have around the intervention and its benefits; the possible burden of the intervention due to the amount of changes needed and length of the study; their feelings if for different reasons they are not able or decide not to fully adhere to the intervention; and that participants may need to prioritize these behaviors recommended by Lethe instead of other activities or preferences that may be relevant to them. The end of the study (and therefore of their participation in the intervention) can also have an important impact on the participant's wellbeing. Members felt that the provision of support and information before, during and after the study would be key for addressing these issues.

5.1.5 Diversity and inclusion

There were discussions around the need for diversity and inclusion in the study. The intervention should be tailored to participants' needs and ensure that different people with different needs and experiences are included and that *"nobody is left behind".*

- *We need to personalise and consider that people are different, make sure this is ok for a diverse set of people. People should not be seen in a collective but individually. I do not want to be put in*

a box. Everybody is different and it is important to see these differences and the diversity of people with dementia.

- *The Lethe project goes for "healthy ageing" it concerns people who are ready to go along with the intervention.*

There were also concerns regarding the people who would join the study and how to ensure that people who are more vulnerable or less likely to be involved in research could also have the chance to participate. It was discussed that sometimes the people who may need most this type of interventions, may be as well less proactive or motivated and this may result in them not participating or at least been informed about the study and having a choice.

- *Something that I like to consider the way in which the enrolment will be made. It should be of really great concern the way the enrolment will be done. I mean, how these people will be picked up? Through some, let's say, publicity or through the hospitals because the people with dementia are in charge of some doctors in the hospital. I mean, the way in which they will be selected is something that for me is very important to consider. (…) It is so general, 40 people from each country, so, where are they? How can we reach these people that have a higher risk of dementia so they will be informed that they can adhere to and participate? (…) It is a big country, I suppose there are many people at higher risk, so how can we sure that these people are informed or how can we recruit them or how can we give them the possibility to participate?*
- *Often it is the people who are the poorest who suffer from the most illness so that's (the cost of healthier lifestyle) a problem for reaching them.*
- *It may not reach the people who will need it the most.*
- *Effective dissemination may also help to reach and activate people who otherwise would not be exposed to research programs and trials.*

There were in particular concerns about people who are less well educated or are from low socio-economic backgrounds. On the one hand, as some of these lifestyle changes may be perceived as been costlier. Eating fresh vegetables, fruit and fish or going to the gym can be quite expensive and some people may not be able to afford this. It is also important to think that some people may feel bad or be blamed if they don't do these changes as they may feel that they are not actively making as much as they can to reduce their risk. But also, on the other hand, as people who are less well-off may be less internet and technology literate and less familiar or prone to the use of technology.

- *A different lifestyle costs a lot of more money than the lifestyle I had. You have to buy fresh vegetables, biological food, that is a lot more money than when you eat the way you used to eat. Not every person can afford that. This is what I heard from the people around me: I can't pay that money.*
- *For this study as it is at the moment, I cannot see any access for people with lower socio-economic background.*
- *The level of education or internet is the problem. I don't see how can be these people included in the study. The point is that if they don't have access or if they lack access or if they are not familiar, and this is a reality in my country, I don't see how we can create this inclusion. My point was to try to reach as many people as possible but with these limits. The problem is the education account.*
- *First of all, I think this social and economic background is very important point of view in this research. In my country, there are big differences between different groups. It would be even more important to get something done with the people with low social and economic background. For instance, how*

do you exercise? When you have money, you can have a personal trainer, when you don't have, you don't use. Really problematic this issue. I think also this is important but how can you do it? To get enough people from different backgrounds It is important to try. I think that ethically and practically is important to try that people from low socio and economic backgrounds join. So, it this would be only for well-off people it would not have been right.

It was also highlighted that efforts should be made to reach these more difficult-to-reach people who may be less well-off and perhaps may have less opportunities to be involved in these interventions.

- *I think, let's say, it is much easier let people participate for people with more possibilities. But if you want to go to people from lower socioeconomic background or education, you could go to the seniors and create groups. (…) this could be because then you could reach these people which need maybe to have some help.*
- *We thought if you could provide all participants with the necessary equipment for the duration of the study. And, in some cases, it would be necessary and assistant. There are people with memory problems, you have to remind them. This is one of the problems. It is very important to make instructions simple and clear so that people with less education or low incomes can also participate. I think, and this is my opinion, the way Lethe is designed there is much exclusion for people.*
- *I don't see very much the economic problem. It is not that it is expensive, the problem is that this group is not digitalized educated, so they are excluded. Maybe the next generation, will be different, or you can also provide support.*

Conclusion

Interventions to reduce risk, such as Lethe, may not readily attract the people who may need them most. Because of the intervention itself (e.g. healthy diet, sports etc.) and also due to the digital aspects, some people who are less well off, are less educated or do not use technology may be less likely to be involved in this study.

5.1.6 Autonomy and informed decision making for participants in the study

Information

Participants should receive clear information about the study e.g. what is expected from them, for how long and how it would affect their daily lives. Participants may need or want different types of information or information relevant to a different component(s). Participants may need more information about the components of the intervention which may be more challenging for them.

It was also highlighted that the information should be reliable, accurate and that confidentiality, data sharing, and privacy were all issues that needed to be addressed and the participants informed about.

Information during the study was also considered as very important, particularly of their progression and how participating in the study may be impacting their risk reduction.

In addition to the type of information, the relationship with the researcher providing the information was also perceived as very relevant, and it was highlighted that enough time should be dedicated to the provision of information and that participants should be able to ask questions before joining the study.

- *Talk with people; have a conversation about it. This is important for motivation as well. Ask the person if he/she has any questions and what kind of support they need. I would talk it over. You have to embrace them, to get them involved and to offer them something, not only the program but also a buddy, a personal contact.*
- *Real contacts, human contacts. Real contacts with other participants, so they can also talk to each other about effects or something. To embrace the people. Make them enthusiastic.*

In relation to the who should be involved in the process of informed consent, some felt just the participant and the researcher; whereas others, would appreciate having someone else (e.g. a relative) with them when informed about the intervention. It was also raised the issue that not everyone has family or someone they would like to involve in the study. This should not prevent or exclude them from participating. It was also discussed the role of the participants' General Practitioner, some felt the GP would not have the time to be involved or to discuss risk reduction with them, however it was felt that that GPs should be also informed by the researchers as this is the person of reference for health issues.

- *For the information, it should be the researcher and participant. I don't have a family so I would be alone there.*
- *As a researcher, I would give the possibility to bring someone with you. Leave it to the patient who he/she would like to bring to the conversation.*
- *It is good that the GP knows about it, that he knows I'm participating and that I'm taking medicine, because if I have problems, I go to him.*

Feedback from Advisory Board regarding the Informed consent sheet

Four members of the Advisory Board reviewed the 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 (i) including subheadings in the text as this would enhance comprehension and (ii) combining two sections which were around a similar topic (voluntariness and right to withdraw).
- Suggestions also included avoiding the use of acronyms (i.e. Principal Investigator in full instead of PI), using the terms consistently (e.g. study, pilot trial) and making sure lay language is used as much as possible. For example, the term "pseudo-anonymised" 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:
    - Participants could test the various devices and apps in advance of the study so to have a better idea of what is involved.
    - Additional supplementary information could 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 they 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

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.

6 Recommendations

6.1.1 Development of the recommendations

The recommendations were developed based on the feedback provided by members of the Advisory Boards in various online meetings and on some of the aspects which had been addressed in the literature.

The first draft of the recommendations was developed by the Alzheimer Europe team and were circulated to members of the Lethe team. Furthermore, four members of the Lethe Advisory Board provided additional feedback and suggestions which were included in the final set of recommendations.

The text below includes a summary of the feedback provided by AB members:

- Overall, all AB members were very positive about the recommendations and found them comprehensive and very relevant.
    - *It is a very interesting and detailed document.*
    - *On the whole I would say that the text is very clear and understandable and the content important.*
    - *The document addresses all the issues I consider to be important in this kind of trial. It is complete and understandable too.*
    - *This is comprehensive and fine.*
- The development of this type of recommendations was perceived as reflecting the strong commitment and relevant work of the Lethe team when preparing the study.
    - *Interesting to see (as a layman) how complete work you are doing when preparing the incoming study*.
- There were some suggestions to clarify some of the recommendations (e.g. to whom the recommendation referred to), some small editing and suggestions to change of a few words which they did not understand (e.g. co-morbidities).
- One of the members suggested to ensure that the positive aspects of the study were also reflected.
    - *Given the usual emphasis on concerns and risks I hope that there is a similar effort along how your story tells about the benefits of digitising the study and the overall benefit to society in participating in the study.*
- Two members highlighted the recommendations which in their opinion were of particular relevance:
    - *I consider very important any attempt to avoid the stigma commonly related to dementia and the fair representation of diversity.*
    - *Especially important recommendations are the ones related to: (i) participants' understanding of, expectations and hopes about risk and the intervention; (ii) avoiding the use of language which is technical or legalised; (iii) avoiding to unnecessarily burden participants with apps, questionnaires or other demands; (iv) ensuring that no one is discriminated from joining the study due to the use or access to technology, financial issues or attitudes to/ concerns about technology.*

6.1.2 Recommendations for the Lethe team

The final set of recommendations are grouped around four different topics:

1. **<u>Providing information and promoting a clear understanding of the intervention and its possible implications</u>**

<u>Potential participants and the broader society</u>

- The Lethe team should be cautious and take into account potential misconceptions about dementia when presenting/providing information about the study.
    - They should avoid making dementia the sole focus when discussing the project due to stigma or fears that arise from being associated with 'dementia-prevention' strategies. A broader focus that also makes use of the term 'brain health' is recommended.
    - The team should clearly explain that dementia risk can be reduced by acting upon modifiable risk factors and clarify misconceptions about one's dementia risk being 'set in stone'. False expectations and hopes should, however, be avoided.
- The Lethe team should provide information about the societal benefits of addressing brain health conditions and dementia and how risk-modifiable interventions may help in this regard and address equity/social justice concerns.
- Careful consideration should be given to how the information about the two groups in the study (active and control) is presented to the potential participants and how this may impact on their expectations and hopes.
- Potential participants should receive appropriate and clear information about the study (e.g. what it involves, privacy issues, risks and benefits) which enable them to make an informed decision about joining (or not) the study.
- The findings of the Lethe study should be broadly disseminated to the general public in an accessible and positive manner.

<u>Participants in the Lethe study</u>

- The Lethe researchers should ensure that participants have a clear understanding of risk and the consequences of high risk and risk reduction approaches for their current and future health (this includes clarifying terms such as modifiable versus non-modifiable risk factors, risk reduction, etc.).
- The Lethe researchers should ensure that the participants have expectations which are feasible and realistic about risk reduction and management.
- The Lethe researchers should support participants when receiving information about their own risk and provide information about how they can discuss about this with other people (if they wish so).

- The participants should be clearly informed about the length of the study, their involvement and its benefits and risk.
- There should be enough time for participants to receive the information, ask questions and a clear point of contact throughout the length of the study.
- Participants should be provided with lay accessible summaries of any text which is too long or too technical (e.g. privacy policies).

- The use of technical, academic or legalised language should be avoided in participant-facing materials.
- There should be clear and visible information about which aspects of the intervention and technology are "optional". Participants should have as much choice as possible in this regard at the beginning of the study and during the whole duration and be aware of how-to de-install / switch off any parts of the app which they don't feel comfortable with.

- The Lethe researchers should provide clear and comprehensive information about the safeguards and measures taken to ensure data protection in the study.
- The Lethe researchers should be particularly attentive to the parts of the information which are more complex or difficult to understand, which affect participants' data (how is collected, stored or shared) and ensure that the information is presented in a clear and accessible manner and that the possible consequences of this for them are clearly presented.
- Clear information should be provided to participants about the different types of data collected passively and actively, by which device, and how it will be stored and used.
- Participants should receive information about their progress and how this is impacting their risk in a manner which is clear, accessible, non-threatening and meaningful to them.

- All participants should receive clear, accessible information about the results of the Lethe study and the implications of this for their health.

2. <u>Offering support and protecting participants from harmful or burdensome situations</u>

- The apps developed and devices used for the study should be tested by end users (e.g. older people at risk) before using them for the study and ensure they are accessible and user-friendly.
- The Lethe team should closely monitor the possible negative impact of the use of technology on participant wellbeing.
- The information that participants receive during the study, and that received by participants who may have more difficulties engaging with the different components of the intervention, should be phrased such that it does not result in the person feeling blamed or as if he/she was not doing enough or doing something wrong.
- The Lethe team should develop mechanisms or strategies to detect, early on, feelings of discomfort, frustration or anxiety which may be caused by the use of technology and could affect the wellbeing of the participant.
- The Lethe team should be attentive to the impact of the intervention on the participants' life and ensure it is not overwhelming or burdensome.
- Participants should have a choice about the different parts of the intervention, apps and questionnaires which have to be completed and be aware of how to switch off any app or questionnaire which they don't feel comfortable with. This should be considered prior to joining the study but also during the study duration.
- The Lethe team should ensure that all participants have all equipment/ devices required for joining the study and that these are replaced in a timely manner if there is any malfunction or the device is not working properly.
- Participants should not be burdened with apps, questionnaires or other aspects of the intervention or technology which are not reasonable or do not have a clear impact on the study goals.

- The Lethe team should ensure that the monitoring required for the study is not too invasive and should consider aspects related to the privacy of the person and issues that may be perceived as sensitive by the participant (e.g. social contacts, GPS, sleeping).
- The Lethe team should promote that participants engage in social contact both with and without the use of technology.
- Participants should be reminded that having a study partner is beneficial for the study but that they can still participate if they don't.
- The Lethe team should promote an autonomous use of the apps and devices and also offer and promote different types of support to participants including peer support and support by the local teams, in a tailored and individualised manner.
- There should be enough time for participants to receive the information, ask questions and there should be a clear point of contact throughout the study.

3. **Ensuring that the study objectives meet participants' needs in a real-world context and after completion of the study**
   - The Lethe intervention should be flexible and adapted to participants' needs, wishes and preferences.
   - The Lethe team should consider participants' current use of strategies and apps for brain health and discuss with them how to integrate them in the intervention/app, so to avoid duplication or burden.
   - The Lethe team should consider and address how other co-existing health conditions of the participants may affect the different parts of the intervention.
   - The Lethe team should consider participants' current use of strategies and apps for brain health and discuss with them how to integrate them in the intervention/app, so to avoid duplication or burden.
   - The Lethe team should carefully consider the impact of the end of the study for participants and help the participant identify existing resources in their community (e.g. GP, social worker) who could support them in continuing with the intervention.
   - Participants in the non-active group should be also offered further access to some of the activities planned for the active group that they could do on their own (i.e. non-guided).
   - The Lethe team should provide some form of ongoing support to participants after the end of the study.

4. **Addressing inequality in access and safeguarding a diverse, non-stigmatising and inclusive environment**
   - The images and information provided in the study and to the general public should reflect the diversity of older people.
   - The terms, images and information provided should be positive and non-threatening.
   - Stigmatising language or images about dementia or cognitive decline should be avoided.
   - The Lethe team should ensure that the intervention and what is required of participants is culturally sensitive and appropriate, for example, in relation to diet or other social aspects.
   - The Lethe team should ensure that the digitalization of the intervention does not prevent older people from participating in the study.
   - The Lethe team should ensure that the financial situation of a person would not prevent him/her from joining and participating in the study.

- The Lethe team should make sure that more vulnerable or disadvantaged groups of older people are also informed, encouraged to join the study and supported if appropriate.
- Efforts should be made to reach out to populations that are less likely to be involved in research by contacting gatekeepers or other means.
- The Lethe team should plan for strategies and accommodations to ensure that people who are less open to the use of technology or have more concerns about its use, but could benefit from this type of interventions, have opportunities for addressing their concerns and participating in the study.

7 References

1. Alpinar-Sencan Z and Schicktanz S (2020) Addressing ethical challenges of disclosure in dementia prediction: limitations of current guidelines and suggestions to proceed. *BMC Med Ethics* 21, 33. https://doi.org/10.1186/s12910-020-00476-4
2. Alzheimer Europe (2010) *The ethical issues linked to the use of assistive technology in dementia care*
3. Alzheimer Europe (2011) *AE Survey: The Value of Knowing*, retrieved from https://www.alzheimer-europe.org/resources/publications/2011-alzheimer-europe-survey-value-knowing
4. Bhopal RS (2016) *Concepts of Epidemiology: Integrating the ideas, theories, principles, and methods of epidemiology* (3 ed.) UK: Oxford University Press
5. Busch, P. A., Hausvik, G. I., Ropstad, O. K., and Pettersen, D. (2021). Smartphone usage among older adults. *Comput. Hum. Behav.* 121, 106783. doi: 10.1016/j.chb.2021.106783
6. Fietkiewicz KJ and Ilhan A (2020) Fitness Tracking Technologies: Data Privacy Doesn't Matter? The (Un)Concerns of Users, Former Users, and Non-Users. *Proceedings of the 53rd Hawaii International Conference on System Sciences.*
7. Gallistl V, Rohner R, Seifert A, Wank A (2020) Configuring the Older Non-User: Between Research, Policy and Practice of Digital Exclusion. *Social Inclusion*, 8 (2):233–243 DOI: https://doi.org/10.17645/si.v8i2.2607
8. Golant, SM (2017) A theoretical model to explain the smart technology adoption behaviors of elder consumers. *J Aging Stud*, 42: 56–73.
9. Gomersall T, Astell A, Nygård L, Sixsmith A, Mihailidis A, Hwang A. (2015) Living with Ambiguity: A Metasynthesis of Qualitative Research on Mild Cognitive Impairment. *Gerontologist*, 55(5):892-912. doi: 10.1093/geront/gnv067. Epub 2015 Aug 27. PMID: 26315317; PMCID: PMC4580312.
10. Hänninen R., Taipale S., Luostari R (2021) Exploring heterogeneous ICT use among older adults: The warm experts' perspective. *New Media Soc* 23:1584–1601. doi: 10.1177/1461444820917353
11. Horstkötter D, Deckers K and Köhlerb S (2021) Primary Prevention of Dementia: An Ethical Review. *Journal of Alzheimers Disorders,* 79(2): 467–476.
12. Keenan AJ, Tsourtos G, Tieman J (2021) The Value of Applying Ethical Principles in Telehealth Practices: Systematic Review. *J Med Internet Res*, 30;23(3):e25698. doi: 10.2196/25698. PMID: 33783366; PMCID: PMC8044738.
13. Kino S, Bernabé E, Sabbah W (2017) Socioeconomic inequality in clusters of health-related behaviours in Europe: latent class analysis of a cross-sectional European survey. *BMC Public Health*, 23;17(1):497. doi: 10.1186/s12889-017-4440-3. PMID: 28535751; PMCID: PMC5442654.
14. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. (2020) Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *The Lancet*, 396(10248):413–46.
15. McGirr A, Nathan S, Ghahremani M, Gill S, Smith EE, Ismail Z (2022) Progression to Dementia or Reversion to Normal Cognition in Mild Cognitive Impairment as a Function of Late-Onset. *Neuropsychiatric Symptoms Neurology*, 98 (21) e2132-e2139; DOI: 10.1212/WNL.0000000000200256
16. Milne A (2010) Dementia screening and early diagnosis: the case for and against. *Health, Risk & Society*, 12, 1, 65– 76.

17. Milne R, Diaz A, Badger S, Bunnik E, Fauria K and Wells K (2018). At, with and beyond risk: expectations of living with the possibility of future dementia. *Sociology of Health & Illness*, 40(6): 969-987. DOI: 10.1111/1467-9566.12731
18. Ottoy J, Niemantsverdriet E, Verhaeghe J, De Roeck E, Struyfs H et al. (2019) Association of short-term cognitive decline and MCI-to-AD dementia conversion with CSF, MRI, amyloid- and 18F-FDG-PET imaging. *NeuroImage: Clinical*, 22:101771. doi: 10.1016/j.nicl.2019.101771. Epub 2019 Mar 13. PMID: 30927601; PMCID: PMC6444289.
19. Owonikoko TK (2013) Upholding the principles of autonomy, beneficence, and justice in phase I clinical trials. *Oncologist*, 18(3):242-4.
20. Schicktanz S and Schweda M (2021) Aging 4.0? Rethinking the ethical framing of technology-assisted eldercare. *HPLS* 43, 93 https://doi.org/10.1007/s40656-021-00447-x
21. Solomon A, Stephen R, Altomare D, Carrera E, Frisoni GB, Kulmala J, Molinuevo JL, Nilsson P, Ngandu T, Ribaldi F, Vellas B, Scheltens P, Kivipelto M (2021) Multidomain interventions: state-of-the-art and future directions for protocols to implement precision dementia risk reduction. A user manual for Brain Health Services – Part 4 of 6. *Alzheimer's Research & Therapy*. https://doi.org/10.1186/s13195-021-00875-8
22. Stites SD, Milne R, Karlawish J (2018) Advances in Alzheimer's imaging are changing the experience of Alzheimer's disease. *Alzheimer's & Dementia*, 10: 285– 300.
23. Thaipisuttikul P, Jaikla K, Satthong S, Wisajun P (2022) Rate of conversion from mild cognitive impairment to dementia in a Thai hospital-based population: A retrospective cohort. *Alzheimers Dement (NY),* 31;8(1):e12272. doi: 10.1002/trc2.12272. PMID: 35386122; PMCID: PMC8970424
24. Ursin F, Timmermann C, Steger F (2021) Ethical Implications of Alzheimer's Disease Prediction in Asymptomatic Individuals through Artificial Intelligence. *Diagnostics,* 4;11(3):440. doi: 10.3390/diagnostics11030440. PMID: 33806501; PMCID: PMC7998766.
25. Van der Schaar J, Visser LNC., Bouwman FH et al. (2022) Considerations regarding a diagnosis of Alzheimer's disease before dementia: a systematic review. *Alz Res Therapy.* 14, 31 https://doi.org/10.1186/s13195-022-00971-3
26. Visser LNC, Minguillon C, Sánchez-Benavides G et al. (2021) Dementia risk communication. A user manual for Brain Health Services—part 3 of 6. *Alzheimer's Research & Therapy,* 13, 170 https://doi.org/10.1186/s13195-021-00840-5
27. Wallace L and Brayne C (2022) The need for a better global dementia response. The *Lancet Neurology*, 21(2):115-116. doi: 10.1016/S1474-4422(21)00459-2.
28. Wang S, Bolling K, Mao W, Reichstadt J, Jeste D, Kim HC, Nebeker C (2019) Technology to Support Aging in Place: Older Adults' Perspectives. *Healthcare*, 10,7(2):60. doi: 10.3390/healthcare7020060. PMID: 30974780; PMCID: PMC6627975.
29. Wangmo T, Lipps M, Kressig RW et al. (2019) Ethical concerns with the use of intelligent assistive technology: findings from a qualitative study with professional stakeholders. *BMC Med Ethics*, 20, 98. https://doi.org/10.1186/s12910-019-0437-z
30. WHO (2019) *Risk reduction of cognitive decline and dementia: WHO guidelines*. Geneva: World Health Organization
31. Wu YH, Damnée S, Kerhervé, H, et al. (2015) Bridging the digital divide in older adults: a study from an initiative to inform older adults about new technologies. *Clin Interv Aging*, 10: 193–201.

8 Appendix

This appendix includes, as an example, the background materials which members of the Advisory Board received in advance of the meeting on ethical issues linked to the project.

Similar materials were sent to members prior to each meeting.

LETHE ADVISORY BOARD

Meeting 11 May 2022

If you have any questions about the meeting or the information in this document please contact: ana.diaz@alzheimer-europe.org

These are the pre-reading materials for the Lethe Advisory Board meeting on 11 May.

This document has been prepared to provide some background information that could help you to participate in the meeting.

We have to plan two groups, please see below times and members:

- Group 1: 10:00 -11.45 CET - Members:
- Group 2: 15.00-16.45 CET - Members:

You don’t need to look at or find any additional information. If anything is unclear, please do not hesitate to contact us and we can provide further details or have a phone call to respond to questions you may have.

Thanks in advance for your time and help with this

A brief reminder about Lethe

The project

Lethe is a European-funded project. Lethe is interested in how we can predict risk of cognitive decline and help to reduce such risk by making changes in lifestyle.

To do this, Lethe is building on the FINGER intervention (an intervention for risk reduction developed in Finland and Sweden and tested in many countries). Lethe will help to understand how some parts of the FINGER intervention could be implemented or measured using technology. The technology involves:

- existing devices (e.g. FitBit smartwatch, some existing apps, online cognitive training programme,) and
- the Lethe mobile phone app which provides access to the different apps and some questionnaires that participants will need to complete.

The Lethe study

- To understand how the technology could be used, we plan a research study which will be conducted in Austria, Italy, Sweden and Finland.
- 160 people will participate in the study (40 in each country).
- Participants will have increased risk of cognitive decline but should not have dementia or a significant cognitive impairment.
- In each country, half of the participants will participate in the "active group" (structured intervention) and the other half in the "non-active group" (self-guided intervention). This is done randomly, which means that neither the researcher or the participant will be able to decide to which group the participant is assigned.
- Participants in the active group will follow an intervention to reduce their risk of cognitive decline which include the following components: nutrition, exercise, cognition, social life, sleep, relaxation, and management of cardiovascular risk factors. Participants in the non-active group will receive information about brain health and suggestions of how to reduce their current risk.
- All participants will receive a Fitbit smartwatch (to be worn day and night) and will be invited to study visits with the study nurse or other health professionals. The participants in the active group will also have access to the Lethe app and intervention. For this they can use their own phone (only android users) or if they prefer, they can use an Android phone from the study.

- At the end of the study, participants will be asked to return the Fitbit, smartphone (if they were using one from the research) and will no longer have access to the Lethe app or activities.

About the meeting on 11 May

The topic of the meeting

During the next meeting of the Lethe Advisory Board in May we would like to address some of the potential ethical considerations of relevance to the project.

The term "ethics" refers to standards which tell us how we ought to act in various situations and how we ought to live with one another. This is often framed in terms of rights, obligations, duties, benefits to society, fairness or specific virtues. These standards of behaviour are based on perceptions of right and wrong or good and bad. Ethics is not just about big societal issues like immigration, war, abortion or euthanasia that are discussed in the media. Everyday matters, as well as actions and decisions made by researchers, policy makers and healthcare professionals, can also have an ethical dimension. How these issues are approached by individuals, groups and societies may have implications for how we see ourselves (i.e. as a good or bad person or society). Behaving ethically in all domains requires a lot of reflection and a willingness to question a lot of the things that we take for granted (e.g. when we sometimes think "that's just the way it is" or "that it has always been like that").

We are interested in your thoughts, feelings and beliefs about things you might consider ethical or unethical in relation to the Lethe project (in the sense of what you consider right and wrong, good and bad or fair and unfair). Don't worry about whether something is technically an "ethical issue" or not.

We will use your feedback to develop some recommendations for the researchers and technical team.

Before looking at the questions which the Lethe team has prepared:

- **What are in your opinion the more relevant ethical considerations, linked to the Lethe study, that the researchers should consider?**
- **Do you have any concerns or issues that you would like to address?**

The questions that we plan to address in the meeting

We have identified the following considerations / questions that we think should be considered in a study like LETHE:

SECTION 1

Data sharing, data privacy and confidentiality

During the study, the researchers will be collecting different type of data and from different places.

- In the study visits: participants will provide detailed health information, complete questionnaires and will have blood tests.
- Devices: participants will use a Fitbit (smartwatch), the Lethe app and other apps.
  - The LETHE app will be specifically designed by the research team for the purposes of this study. However, we plan to also use some other existing apps (e.g. the relaxation/meditation app) which are already commercially available apps developed by an external company and not linked to the study.
  - Some of the information will be collected passively (e.g. Fitbit will record automatically some of the information) and some, actively (e.g. the participant will enter the information such in the case of nutrition, goals, etc.).
- For using some features in Fitbit (e.g. google assistant) the participant will need to use a Google account.

Examples of the information which will be collected include:

- Fitbit: step count, physical activity level, different sleep parameters, pulse, heart rate. Location information (where the person is). Age, birthday, height, weight, gender.
- Google account: email and name
- LETHE app: the different questionnaires will collect some dietary habits, mood, symptoms of stress or depression, and information about when and how often the app/phone is used (time stamps).
- Other apps: it is not clear yet as the researchers have not finalised the selection. This may include existing messaging apps e.g.WhatsApp and an app for meditation.
- RADAR-base platform: this is an existing open source platform; the LETHE system will utilize this platform as a mediator to collect activity and physical measurements from Fitbit. In the privacy policy of RADAR-base it is stated that it is GDPR compliant and the data from RADAR-base stays only within the EU.

The information collected in the study visits and by the Lethe app will be stored directly in the EGI data servers (EGI is the company in Lethe in charge of that). This information will be used for the purpose of the study and will be accessible only to study partners.

The information from Fitbit will be first collected and stored by Fitbit (as it would be the case for any user of Fitbit). The Lethe team will be able to access this information from Fitbit and will also store this information in the EGI data servers.

All data collected in the EGI data servers will be processed and stored separate from any personal identifiers, so each participant will receive a random study ID. When the data will be analysed and reported, no individual will be recognized.

Fitbit or Google will not be able to access any of the data entered in the LETHE app or collected during the visits. So, all the information collected directly by the LETHE researchers (e.g., questionnaires, cognitive/other medical data) will not be transferred to or shared with any external app providers / services.

Participants will be asked to read and will have to accept the company's (e.g. Fitbit) or app provider's own terms and conditions and privacy policy in order to enrol in the study. If the person does not accept (e.g., Fitbit terms) it will not be possible to participate (since this is such as essential part of the study).

These policies about privacy and terms are often in English and not in the participants' local language (e.g. in Fitbit). In some cases, these documents mention that data might also be transferred outside the European Union.

Questions for the Advisory Board

- How do you feel about this?
- What concerns do you think participants may have? How can reassure participants about these issues?
- What kind of information should participants receive?
- If for any device, the participant needs to use a "google account", the research team is considering two different possible approaches:
  1) Ask the participant to use his/her personal google account. In this case, some personal information (e.g. name and email address) will be collected by Google. In this case, certain functions of the LETHE app (like the calendar) would be synchronized with the Google calendar (if the participant is already using one)
  2) LETHE could create google accounts and then "assign" them to the participants, in that case, participants would not need to enter their own name and email address. This would involve an additional account and email for the participants which is not

their regular one. In this case all the data that is collected by LETHE and third parties could not be connected to an individual person.

Do you have a Google account? What are your views on both options?

- For Fitbit (and the apps which have not been developed by Lethe), the Lethe legal experts have drafted the explanation below. Is the information clear and sufficient?

  Text:

The 'Lethe Consortium' uses 'Fitbit' devices to record and collect your data. These devices are 'owned' by the 'Lethe Consortium' however, they are manufactured and use services provided and controlled by 'Fitbit'. The 'Fitbit' devices record your raw data, then 'Fitbit' processes them in their systems and finally share them with 'Lethe Consortium' based on your consent. During the recording, processing and up to the sharing stage (a) privacy policy and (b) terms of service apply as set by 'Fitbit'. - Terms of Service > (https://www.fitbit.com/global/us/legal/terms-of-service) - Privacy Policy > (https://www.fitbit.com/global/us/legal/privacy-policy)

- We plan to store and keep the data for 10 years, how that this sound to you?

SECTION 2: Issues related to communication

We would like to discuss about the terminology that is usually used to talk about risk (e.g. risk reduction, prevention, brain health etc)

- What comes to mind when you hear these terms: prevention of dementia, brain health and risk reduction
- Which one(s) do you prefer? Is it there any that you don't like?
- What are the possible benefits and challenges of using each of these terms?

We would also discuss the kind of language that should be used when presenting information to the participants, when talking about them, and when presenting the intervention and their results to the general public.

- What advice would you have for the researchers and people working on communication in the project?
- Is there any particular term to avoid?
- What would be helpful for participants and for the general public?

SECTION 3: Stigma

Stigma is a complex social phenomenon which consists of groups of people being singled out and labelled on the basis of a shared attribute or characteristic that is recognisably different in some way and considered socially significant. People from these groups are then considered as having less value and are discriminated against. The Lethe project and study promote the idea of healthy ageing, which is very positive. However, using terms like "healthy ageing" as something to aspire to could also be associated with labelling, discrimination and blame (e.g. for people who do not share this goal/interest, do not feel able to achieve it or develop a disease).

- What are your views on this?
- What could you recommend to address this?

SECTION 4: Inclusion and diversity

This includes issues around the potential exclusion of people who are marginalised. This typically includes people from a lower socio-economic background, with lower levels of education and, who are not as familiar/comfortable with Internet or who lack access to it. Often the imagery surrounding "healthy ageing" portrays smiling, White, middle-class, heterosexual couples with grandchildren. Certain groups of people (e.g. people from some minority ethnic groups, LGBT+ couples, single people with no children etc.) may have difficulty relating to such a concept when portrayed in this way and consequently be excluded from any potential benefits of it.

- What are your views on this?
- How could we promote diversity and inclusion in the study?
- How could we support / engage with people from minority or marginalised groups?

SECTION 5: Beneficence and promoting wellbeing

Participants will be using some devices (e.g. Fitbit, app), will attend some visits with the researchers and will take part and be supported on making important life style changes for 18 months. During this time, they will have access to the different parts of the intervention (class exercise, cognitive training, advice etc).

- How could we support participants so they don't feel left on their own once the research is finished (e.g. as they need to give back the smartphone, Fitbit and will not have access to the different parts of the intervention like the cognitive training).
- What do you think may be the possible (positive and negative) emotional impact of being involved in this type of intervention (specially with a digital component)?

Thanks!