**Supplementary material**

**Supplementary list of abbreviations**

Aβ-40/42 β-Amyloid 1-40/42

APOE Apolipoprotein E

BDNF Brain Derived Neurotrophic Factor

BNP Brain Natriuretic Peptide

CCT Compassionated Comprehensive Therapy

COPE Carers of Older People in Europe

2D two dimension

DHEAS DeHydroEpiAndrosterone Sulfate

DKI Diffusion Kurtosis Imaging

eCRF electronic Case Report Form

ECRIN European Clinical Research Infrastructure Network

Euclid EUropean CLInical trial platform & Development

FLAIR Fluid-attenuated inversion recovery

GREFEX Groupe de Réflexion sur l'Evaluation des Fonctions Executives, Group of reflexion and assessment of executive functions

γGT Gamma-GlutamylTransferase

GOT Glutamic Oxaloacetic Transaminase

GPT Glutamic Pyruvic Transaminase

GWAS Genome Wild Association Study

HDL High Density Lipoproteins

hsCRP high-sensible C-Reactive Protein

IGF-1 Insulin Growth Factor-1

IQ Intelligence Quotient

LDL Low Density Lipoproteins

MBSR mindfulness-based stress reduction

MMN Mismatch negativity

MMSE Mini-mental state examination

MOS Medical Outcomes Study

NFL Neurofilament

PAI-1 Plasminogen Activator Inhibitor-1

PD-Hpc high-resolution proton-density

PET Positron Emission Tomography

QSM Quantitative Susceptibility Mapping

REST Repressor Element 1-Silencing Transcription factor

FCSRT Free and Cued Selective Reminding Test (RL-RI16 for the French version)

SHBG Sex Hormone Binding Globulin

SOD SuperOxide Dismutase

tPA  tissue Plasminogen Activator

TSC Trial Steering Committee

TSH Thyroid Stimulating Hormone

WAIS Wechsler Adult Intelligence Scale

WMS Wechsler Memory Scale

### 1) Participants recruitment and prescreening

Recruitment started at the end of 2016 and ended in May 2018. Participants were recruited from the general population in and around the town of Caen in Normandy (France) through a communication campaign for the local stakeholders and public, including advertising in media outlets and social media, and with flyers distributed in relevant local events and places. Interested citizens were invited i) to attend a public conference in which the investigators give written and oral information about the clinical trial and ii) to complete an online questionnaire to prescreen the individuals who fit with the main eligibility criteria (age ≥ 65 yrs. old; > 1 year from retirement, etc.). A Questions & Answers period during each conference, and in-person exchanges with the research team were conducted to ensure that potential participants understand the implications of the study and are motivated and available to participate. Prescreened participants were then invited to the screening visit (V0) at which the diagnostic battery depicted in Table 1 is performed.

### 2) Participant pre-inclusion: eligibility criteria and screening visit (V0)

During the screening visit (V0), written and oral information about the trial is provided again and an informed consent form was signed. Then the inclusion and exclusion criteria (detailed in Table 2) were assessed. Briefly, eligible participants are cognitively normal men or women aged ≥ 65 years, with no major neurological or psychiatric disorder, French native speakers retired for at least one year, not speaking English fluently and who had no intensive practice of meditation. Main exclusion criteria were safety concerns in relation to MRI or PET scanning, presence of a major neurological or psychiatric disorder, history of cerebrovascular disease, presence of a chronic disease or acute unstable illness and finally current or recent medication

use that may interfere with cognitive functioning (Table 2). These criteria are verified for each participant through the medical interview with a medical doctor and the diagnostic battery tests with a neuropsychologist (Table 1 for details). The medical doctor performs a general health screening comprising assessment of medical history and medications, measurement of height and weight, hip and waist circumferences and sitting blood pressure.

### 3) Measures collected at the baseline and follow-up visits (V1, V2, and V3)

Measures collected at V1 and V3 include behavioral, neuroimaging, sleep and biological measures (and a selected set of behavioral measures are collected at V2).

Behavioral measures are detailed in Supplementary Table 1, neuroimaging measures in Supplementary Table 2 and biological measures in Supplementary Table 3.

**Supplementary Table 1**: Behavioral measures performed at V1, V2 and V3. **: Questionnaires also given to the participant's partner pertaining to the partner him- or herself; *** Questionnaires also given to the participant's partner pertaining to the participant.

| Domain assessed | Test | Reference | Points of assessment | | |
|---|---|---|---|---|---|
| | | | Inclusion (V1) | 9 months (V2) | 18 months (V3) |
| **Global cognition** | *Mattis Dementia Rating Scale* | [1] | **x** | | **x** |
| **IQ** | *Matrix Reasoning* | *WAIS IV* | | | **x** |
| | *Vocabulary* | *WAIS IV* | | | **x** |
| **Attention / Executive function** | *Attentional Style Questionnaire* | [2] | **x** | | **x** |
| | *Flanker task with spatial cueing* | [3] | **x** | **x** | **x** |
| | *Stroop* | *GREFEX 2008* | **x** | **x** | **x** |
| | *Digit Symbol Substitution* | *WAIS IV* | **x** | **x** | **x** |
| | *Trail Making Test A & B* | *GREFEX 2008* | **x** | **x** | **x** |
| | *D2R (Selective attention)* | [4] | **x** | | **x** |
| | *Digit Span Forward* | *WAIS IV* | **x** | | **x** |
| | *Digit Span Backward* | *WAIS IV* | **x** | | **x** |

| | | | | | |
|---|---|---|---|---|---|
| **Verbal episodic memory** | *California Verbal Learning Test-II version A&B-5 learning trials, short-term recall* | [5] | **x** | | **x** |
| | *California Verbal Learning Test-II version A&B-5 learning trials, long-term recall* | [5] | **x** | | **x** |
| | *Logical memory (paragraph 1, Short-term recall)* | *WMS IV* | **x** | | **x** |
| | *Logical memory (paragraph 1, Long-term recall)* | *WMS IV* | **x** | | **x** |
| **Visual episodic memory** | *Visual Object Separation Task* | [6] | **x** | **x** | **x** |
| **Autobiographical memory** | *Autobiographical Fluency (Episodic & Semantic)* | [7] | **x** | | **x** |
| **Personality** | *The Big Five Inventory* | [8] | **x** | | |
| **Mental imaging** | *2D - Mental Rotation Test* | *Adapted from* [9] | **x** | | **x** |

| | | | | | |
|---|---|---|---|---|---|
| | *Mental visual imaging battery* | *Adapted from* [10] | **x** | | **x** |
| **Language** | *Verbal orthographic fluency : P* | *GREFEX 2008* | **x** | **x** | **x** |
| | *Verbal category fluency : animals* | *GREFEX 2008* | **x** | **x** | **x** |
| **Psychoaffective and emotion regulation** | *State-Trait Anxiety Inventory (STAI)*** | [11] | **x** | **x** | **x** |
| | *Empathic Dictator* | [12] | | | ***x*** |
| | *Geriatric Depression Scale (GDS) - 15 item*** | [13] | **x** | **x** | **x** |
| | *Interpersonal Reactivity Index (IRI)* | [14] | **x** | **x** | **x** |
| | *Positive and negative affect (PANAS-NOW)* | [15] | **x** | **x** | **x** |
| | *Cyberball task and related questions* | [16] | | | **x** |
| | *Penn State Worry Questionnaire - short* | [17] | **x** | **x** | **x** |
| | *Emotion regulation abilities* | [18] | **x** | **x** | **x** |
| | *Rumination Response Scale* | [19] | **x** | **x** | **x** |

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|---|---|---|---|---|---|
| | *SoVT-Rest* | *adapted from* [20] | | | |
| | *Depression Death Scale Revised (21 items)* | [21] | **x** | | **x** |
| **Mindfulness** | *Trait Mindfulness: Five-Facet Mindfulness Questionnaire (FFMQ-15)*** | [22] | ***x*** | ***x*** | ***x*** |
| | *Drexel Defusion scale* | [23] | ***x*** | ***x*** | ***x*** |
| | *Multidimensional Assessment of Interoceptive Awareness (MAIA)* | [24] | ***x*** | ***x*** | ***x*** |
| **Cognitive complaint, quality of life & well-being** | *McNair Cognitive Difficulties Scale Self-assessment of cognitive deficits Cognitive Difficulties Scale* | [25] | **x** | | **x** |
| | *Well-being (7-items version)* | [26] | **x** | **x** | **x** |
| | *Three-Item Loneliness Scale* | *Adapted from the Revised UCLA Loneliness Scale,* [27] | **x** | **x** | **x** |

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| | *Quality of life questionnaire (WHOQOL-BREF)* | [28] | **x** | | **x** |
| | *Satisfaction with life* | [29] | **x** | **x** | **x** |
| **Compassion and prosocialness** | *Self-compassion- short version* | [30]*, adapted from* [31] | **x** | **x** | **x** |
| | *Other Compassion**** | [30] | **x** | **x** | **x** |
| | *The COPE index*** | [32] | **x** | **x** | **x** |
| | *MOS Social Support Survey*** | [33] | **x** | **x** | **x** |
| | *Prosocialness scale**** | [34] | **x** | **x** | **x** |
| **Lifestyle** | *Adapted CAQ and LEQ* | *Adapted from* [35] [36] | | **x** | **x** |
| | *Modifiable Activity Questionnaire (MAQ)* | [37,38] | **x** | | |
| | *Mediterranean diet adherence* | [39] | **x** | | **x** |
| | *The Physical Activity Scale for the Elderly* | [40] | **x** | **x** | **x** |
| | *Cognitive activities questionnaire* | [36] | **x** | | |

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|---|---|---|---|---|---|
| | *The Lifetime of Experiences Questionnaire (LEQ)* | [35] | **x** | | |
| **Sleep** | *Leeds Sleep evaluation questionnaire* | [38] | **x** | | **x** |
| | *Pittsburg Sleep Quality Index Last month* | [41] | **x** | | **x** |
| | *St Mary's hospital questionnaire* | [42] | **x** | | **x** |
| | *Severity of insomnia index* | *[40]* | **x** | | **x** |
| | *Pittsburg Sleep Quality Index 5 last years* | *Adapted from* [41] | **x** | | **x** |
| | *Epworth Sleepiness Scale* | [43] | **x** | | **x** |
| **Medical Questionnaires** | *List of medications, doctor visits, and cardiovascular risk factors* | *Adapted from* [44]*; Recommendations from National Insitute of Alcohol Abuse and Alcoholism* | **x** | | **x** |

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|---|---|---|---|---|---|
| | *Charlson Index* | *[42]* | **x** | | **x** |

**Supplementary Table 2**: Details on the neuroimaging data acquisition parameters and task description.

| | SEQUENCE | MAIN PARAMETERS |
|---|---|---|
| | 3D T1 | Sagittal FFE, RT/ET=20/4.6ms, 256x256, 180 slices, 1x1X1mm$^3$ |
| **STRUCTURAL MRI** | FLAIR | Sagittal 3D-IR Vista, RT/ET=8000/337ms, 250x250, 180 slices, 0.8x0.8X2mm$^3$ |
| | DKI | Axial DWI-SE, 32 dir b=1000 s/mm$^2$; RT/ET= 10000/82ms, 70 slices, 224x224, 2x2X2mm$^3$ |
| | PD-Hpc | Coronal, RT/ET=3500/19ms, 120x120, 13 slices, 0.75x0.75X2mm$^3$ |
| | QSM | |
| **FUNCTIONAL MRI** | Resting-state (T2*) | Axial 2D-T2*-FFE-EPI SENSE, RT/ET=2383/ 30ms, 224x224, 42 slices, 2.8x2.8x2.8mm$^3$ |
| | Task-related (T2*) | Attentional AX-CPT[45]: fMRI acquisitions are obtained during performance on an attentional task allowing to measure during the same scanning session context maintenance, inhibition and sustained attention as well as the recruitment of brain compensatory processes. Series of cue-probe pairs of letters are presented and participants are told to make a target response to an X-probe but only when it follows an A-cue (AX trials). Non-target responses are required on all other trials (e.g., BY trials). Modifying the alternation of A and X letters allow to determine brain areas associated to context maintenance (AX |

| | | |
|---|---|---|
| | | trials) and inhibition processes (e.g., AY and BX trials). Brain areas associated to sustained attention will be explored by comparing first and second part of the task. The recruitment of compensatory processes will be assessed by comparing changes in brain activity between an easy and difficult version of the task. In the difficult version, distractor letters will be presented in another color between the cue and the probe. |
| | | Emotional SoVT-Rest: fMRI acquisitions are obtained during and after exposure to short video clips (10-18 sec) depicting people suffering (high emotion) or people in everyday life situations (low emotion) to measure brain activity and connectivity changes in relation to emotions and the degree to which emotions persist after an emotional event. High and low emotion videos will be presented in blocks of three videos and each block will be followed by a 90s period of rest (similar to the procedure used to measure resting brain activity in [2,3]. Self-reports about empathy, positive and negative emotions during the viewing of each video clip will be collected outside the fMRI. |
| **EEG** | Resting state | EEG power density in theta, alpha, beta and gamma oscillatory bands. |
| | Auditory ERP | Auditory mismatch negativity (aMMN) |
| **PET** | Amyvid | Injection of 4 MBq/kg, acquisition early 0-10min and late 50-60min, 47 slices 2.7x2.7x3.27mm$^3$ |

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| | Glucotep | Injection of 200 MBq, acquisition 50-60min, 47 slices<br><br>2.7x2.7x3.27mm$^3$ |

**Supplementary Table 3**: Details on the blood sampling and analyses.

| Blood Markers | Number and Type of tubes (blood volume) | Type of blood | Specific conditions | V1 | V3 |
|---|---|---|---|---|---|
| Cholesterol<br>Triglycerides<br>HDL<br>LDL<br>Urea<br>Creatinine<br>γGT<br>GOT<br>GPT | 1 Dry (2 mL) | Plasma, serum | Fasting | x | x |
| Glycemia | 1 Fluorinated (2 mL) | Plasma | Fasting | x | x |
| Blood count (12 markers) | 1 EDTA (2 mL) | Total blood | | x | |
| APOE | 1 EDTA (4 mL) | Total blood | | x | |
| REST (cDNA/mRNA)<br>GWAS | 1 EDTA (4 mL) | Total blood | | x | x |
| SOD<br>NFL<br>Biobank (-80°C) | 1 EDTA (4 mL) | Total blood | | x | x |

| | | | | | |
|---|---|---|---|---|---|
| BNP<br>Insuline | 1 EDTA (4 ml) | Plasma | | x | x |
| Estradiol<br>DHEAS<br>Cortisol<br>hsCRP<br>SHBG<br>Bioavailable testosterone<br>TSH<br>IGF-1 | 3 Dry (12 mL) | Serum | Between 8:00 and 10:00 AM | x | x |
| Serotonine Biobank (-80°C) | 1 Heparin (4 mL) | Total blood<br>Plasma | 1 day before of diet (No tomatoes, avocados, pineapple, chocolate, bananas…) | x | x |
| tPA<br>PAI-1 | 1 Citrated (4 mL) | Plasma | | x | x |
| Cytokines<br>BDNF<br>T-Tau & P-Tau | 2 EDTA (8 mL) | Plasma | | x | x |

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|---|---|---|---|---|---|
| Aβ40/42 | | | | | |
| Lymphocyte senescence | 3 Heparin (12 mL) | Total blood | Transfer the day of sampling | x | x |
| Telomeres & Telomerase | 1 EDTA (6 mL) | Total blood | Transfer the day of sampling | x | x |
| | 18 tubes ( 68 mL) | | | 18 tubes (68 mL) | 16 tubes (62 mL) |

AD: Alzheimer's disease; γGT: Gamma-GlutamylTransferase; GPT: Glutamic Oxaloacetic Transaminase; GPT: Glutamic Pyruvic Transaminase; HDL: High Density Lipoproteins; LDL : Low Density Lipoproteins; APOE4: Apolipoprotein E; TSH: Thyroid Stimulating Hormone; BNP : Brain Natriuretic Peptide; hsCRP: high-sensible C-Reactive Protein; E2: Estradiol; SHBG: Sex Hormone Binding Globulin; DHEAS : DeHydroEpiAndrosterone Sulfate; GWAS : Genome Wild Association Study; Aβ-40/42 : β-Amyloid 1-40/42; T-tau : Total Tau; P-tau: Phospho-Tau; tPA : tissue Plasminogen Activator; PAI-1: Plasminogen Activator Inhibitor-1; BDNF: Brain Derived Neurotrophic Factor; NFL : Neurofilament; IGF-1 : Insulin Growth Factor-1; SOD: SuperOxide Dismutase; REST : Repressor Element 1-Silencing Transcription factor.

### 4) Randomization and allocation concealment

The randomization list will be generated centrally by the trial statistician at the European Clinical Trials Platform & Development group (Euclid, Bordeaux, France) prior to the start of the study and kept confidentially in a secure environment. Due to the group-based nature of the intervention, randomization is performed by the study project manager on the same day for all the participants of each cohort, in their order of inclusion (date of signature of informed consent) and after monitoring of eligibility criteria and of their persistent willingness to

continue the study. In order to allow individual disclosure of the randomization result to each participant, individual allocation results (ID number – allocated group) are concealed in sealed envelopes with the participant ID number by Euclid statistician, then sent to the study project manager. All participants of a cohort are then invited to an announcement visit where they receive general and specific information about the next steps of the clinical trial, and their individual envelope.

### 5) Blinding

The trial is observer-blind. All interviewers, psychometrists and outcome assessors involved in assessments are blind to intervention condition. Participants are asked to refrain from referring to the intervention or their intervention condition during these assessments. Blind staff who need to enter participant data into the electronic case report form (eCRF) do not have access to the randomisation website page or any page which might break the blind (including data collected during the intervention).

### 6) Interventions

For both the meditation and the foreign language training interventions, each weekly group session is divided into three parts: presentation of a theme, sharing, and formal practice. The first two sessions of each month include an equal share of these three parts (3x40min), session 3 includes more sharing (30/60/30min) and session 4 more practice (30/30/60). For both interventions, participants benefit from media (manual and audio) for their practice. The media (text, images, audio, video) and activities (alone, in pairs, in groups) rotation help to maintain interest and motivation. In addition, participants have to complete daily practice

runlogs at home and throughout the intervention on an electronic tablet to inform on their practice (duration, nature, difficulty and pleasantness level).

Monthly meetings are organized between the scientific investigators and the teachers of both interventions to optimize the intervention monitoring, and homogeneity. The teachers in charge of the intervention can also contact the scientific investigators at any time to keep them informed about any aspects related to the intervention or to the participants, to ensure that the care and follow-up of the participants are optimal.

a) The meditation intervention

The teaching content of the meditation intervention is shaped in 9 months dedicated to the teaching of mindfulness meditation followed by 9 months dedicated to the teaching of the meditation on loving kindness and compassion. A new educational theme is introduced each month during the first session and is further developed, practiced and discussed in the other sessions of the month.

Mindfulness, or attentive presence, consists of cultivating a vigilant awareness of one's own thoughts, actions, emotions and motivations. The participant learns to intentionally pay attention to his or her internal or external experiences in the present moment, without making any value judgment. The happy mental states (mental calm, compassion) or unhappy mental states (ruminations, difficult emotions) are observed without identifying or being absorbed by these experiences. The aim is that the present moment is lived in a more open and flexible way and is less dominated by mental conditioning that is a source of suffering. Mindfulness-based psychotherapies are effective especially for stress management and the prevention of relapse into depression [48–50]. The mindfulness portion of this program is directly adapted from an 8-month mindfulness-based intervention especially designed for older adults and validated on a group of Francophone older adults [51].

The practice of kindness-based meditation (short for loving-kindness and compassion meditations) is aimed at improving the relationship with oneself and to the world by addressing in a more positive perspective emotions such as shame, self-criticism, or anger, and by developing gratitude and appreciation for positive experiences such as caring love or compassion. Building on the non-judgmental monitoring capacity developed in mindfulness meditation, the participants will learn to cultivate self-acceptance and kindness toward oneself for instance in relation to one's negative thoughts, distractions, difficult emotions, unpleasant physical sensations to foster appreciation toward positive qualities of one's mind (joy, contentment, …). The participants will then learn to extend a similar attitude of care and loving-kindness toward their loved ones, toward neutral persons (e.g. stranger), or toward difficult persons, ultimately recognizing that the need for comfort, security, and happiness is shared by all living beings. The compassion part of this program is directly adapted from the Compassionated Comprehensive Therapy (CCT), an integrated and multimodal psychotherapeutic approach developed in England by Prof. Paul Gilbert [52], and adapted in France by the Prs. Pascal Delamillieure and Francis Gheysen at the University Hospital of Caen in a program called Mindfulness based on Compassion and Insight. The compassion part of this program incorporated also elements from a secular meditation training program named The Joy of Living developed by the Tibetan Buddhist teacher Mingyur Rinpoche [53]. The adaptation and extension of these two programs for the Medit-Ageing study were performed by two of the meditation teachers, Martine Batchelor and Thien Huong Tran (Titi Dolma) in interactions with the scientific team.

There will be one day of meditation with about 5 hours of practice during which participants immerse themselves more intensively into meditation practices.

b) The foreign language training intervention

A positioning test is proposed during the inclusion visit at the end of the diagnostic battery (Table 1) to allow a precise assessment of the initial level of each participant. If the number of participants in the foreign language training group is higher than 15, subgroups of levels based on this test are established to facilitate teaching. A large place is given to the recognition of the concepts discussed in previous courses. The progress of the participants is evaluated according to a training follow-up document and personalized or group-oriented help as needed. A day of practice on the Anglo-Norman island of Jersey is organized where participants have a mission to accomplish with information to obtain on different places, objects to find and items to buy.

c) The passive control group

After V3, participants from the passive control group will have an opportunity to enroll for free either into an 8-week mindfulness-based stress reduction intervention (MBSR), or an 8-week English language training program at the Caen University.

## 7) Statistical analyses

Statistical analyses related to the primary outcome will be conducted on an intent-to-treat principle, (i.e. all randomized participants will be included in the analysis in the group to which they were initially randomized and all their data are used, regardless of protocol deviations during the trial). Moreover, missing primary endpoint data will be handled with a “missing = failure” strategy (i.e. missing data will be imputed as the minimum individual change between baseline pre-intervention and 18 month-follow-up post-intervention visits observed for the corresponding measure across all groups). This strategy will be conservative as it will bias the difference between compared groups downwards. Moreover, a sensitivity analysis will check the robustness of the main analysis to missing data, using an extreme cases strategy. Briefly,

missing data will be imputed with i) a failure of strategy in one group and a success of strategy (maximum change between baseline pre-intervention and 18 month-follow-up post-intervention visits observed across all groups) in the other, and ii) vice versa. The main and sensitivity comparative analyses will be performed with adjustment on baseline prognostic factors (age, education, gender, MMSE). In order to estimate the expected effect of both interventions when received in a sufficient minimal amount, a per-protocol analysis will include only participants who attended at least 20% of their allocated interventions classes (or neither meditation nor foreign language classes if in the passive control group), and with primary endpoints available. An analysis of the effect of the amount of exposure to the intervention (number of hours of practice, number of sessions...) will also be performed.

Secondary outcomes will be analyzed by appropriate statistical tests depending on the nature of the specific outcome measure. Giving the exploratory aim of the secondary objectives, an per-protocol analysis will be performed on available data (missing data will not be replaced). Therefore, the result will be interpreted with cautiousness.

## 8) Ethics and safety aspects

The study complies with the principles of good clinical practice. Participants give their written informed consent before enrolment in the study. The Sponsor (Inserm) of the clinical trial has insurance for all the participants. The disadvantages, risks and adverse events in the present clinical trial are considered as low. Blood samples are drawn from the antecubital vein after disinfection with alcohol swabs. There is a minimal risk of infection and bleeding related to the procedure. There are no known side-effects of a single MRI acquisition, but the procedure can be uncomfortable. A thorough anamnesis is carried out during the medical examination

to account for contraindications (e.g. metal implants). Unexpected findings will be dealt with according to local hospital guidelines.

Transitory unwanted effects have been reported among meditation practitioners [54,55] in particular during intensive meditation retreats [56]. Side effects such as depersonalization and derealisation or depressive symptoms have been reported in psychiatric conditions such as schizophrenia, depression, or following trauma history [57,58]; public clinical guidelines about meditation-related risks are unfortunately still in their infancy [55]. The Oxford Mindfulness Centre and the University of Massachusetts Center for Mindfulness have published recommended exclusion criteria for standard mindfulness-based intervention, excluding current suicidality and/or any current psychiatric disorder [57,58].These exclusion criteria are followed in the present clinical trial. Two of the meditation teachers are psychiatrists and will detect possible adverse events due to the intervention. In this case, participants are offered a consultation with experienced psychiatrists. Meditation-related side effects will be documented. Individual pausation, temporary adjustments or discontinuation of the intervention is decided in collaboration between the physician, study staff and the participant, and will be reported.

## 9) Study governance and monitoring

The management structure of Medit-Ageing, as defined by the Medit-Ageing consortium and illustrated in Figure 3, includes the coordinator (G Chételat), the project management team (Management workpackage) and the executive committee, as well as 6 scientific workpackages and 2 transverse workpackages. This management structure has the

responsibility to monitor and ensure the project overall progress and to take and implement the strategic, scientific and technological decisions made by the consortium.

The sponsor (Inserm) has established a trial steering committee (TSC) according to Good Clinical Practice guidelines with the responsibility to i) provide oversight of the conduct of the trial, ii) advise on scientific credibility on behalf of the sponsor and the funder, and iii) to assess the progress of the protocol. The trial steering committee (TSC) consists of the coordinating investigator, the scientific lead, work package lead representatives of the Medit-Ageing European Project, sponsor representative, European Clinical Research Infrastructure Network (ECRIN) representatives, EUCLID representatives, and independent experts. The TSC will ensure that the trial is conducted to the rigorous standards set out in the GCP and ethical guidelines. The TSC will review safety data and has the authority to stop the trial according to study-specific agreed criteria.

The sponsor of the trial will act as data controller, according to the European Directive on the protection of individuals with regard to the processing of personal data and on the free movement of such data, in compliance with the Directive 95/46/EC of the European Parliament and of the Council (Official Journal L281, 23/11/1995, p. 0031-0050) at all stages of data management.

The investigator project manager dedicated to this study is in charge of data management at the first level under the responsibility of the Principal Investigator. The eCRF is completed after each study visit. The software used for data management is Ennov Clinical, from the Ennov company (Paris, France), version 7.0 or any later version. Consistency checks are programmed by the EUCLID data manager in order to check the consistency and the completion of data in the eCRF. The list of consistency checks is predefined by the project team and then passed on to the data manager. For specific data as imaging, polysomnography and somnoart® data for

example, they are not managed via the eCRF but independently via dedicated and secured tools and storages.

An external Data and Safety Monitoring Board (DSMB) independent of the sponsor was also appointed. The DSMB is responsible to evaluate and to advise the investigators on the safety of the participants included in the Age-Well trial. The membership of the DSMB and the responsibilities of the DSMB and the sponsor were defined in a separate document entitled the 'Data and Safety Monitoring Board Charter'. The DSMB Charter included information about data flow, purpose and timing of DSMB meetings, communication strategy, procedures for ensuring confidentiality, procedures to address conflicts of interest and statistical monitoring guidelines.

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