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Complete List of Authors:	Dimachki, Samar; Université Lyon 2, Laboratoire d'Etude des Mécanismes Cognitifs Tarpin-Bernard, Franck Croisile, Bernard; Hospices Civils de Lyon Chainay, Hanna
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Low to high intensity computer-based cognitive training at home in supplement to standard care in AD patients: protocol design

Samar Dimachki[1,3], Franck Tarpin-Bernard[3], Bernard Croisile[2] & Hanna Chainay[1]

[1] Université Lyon 2, Laboratoire d'Etude des Mécanismes Cognitifs

[2] Hôpital Neurologique, Hospices Civils de Lyon

[3] Scientific Brain Training SA

samar.dimachki@univ-lyon2.fr

f.tarpin@sbt-human.com

bernard.croisile@wanadoo.fr

hanna.chainay@univ-lyon2.fr

Corresponding author : Samar Dimachki

Université Lyon 2

Laboratoire d'Étude des Mécanismes Cognitifs

5 avenue Pierre Mendès France

69676 Bron, France

e-mail : samar.dimachki@univ-lyon2.fr

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Abstract

Introduction: Recent studies on cognitive training carried out with Alzheimer's disease (AD) patients showed positive long-term lasting effects of training on cognition and activities of daily living and suggested conceiving remote computer-based programs to increase training sessions while reducing patient's travelling. The main objective of this study is to examine short- and long-term benefits of computer-based cognitive training in mild to moderate AD patients realized at home, as a complement to the training carried out in speech and language therapist (SLT) offices. The secondary purpose is to study training frequency required to obtain noticeable effects.

Methods and analysis: This is a national multi-center study, taking place in SLT offices. The AD patients follow training in one of the three conditions: once a week in SLT office only (as usual condition) and once a week in SLT office plus one or three times per week at home. The effects of training at home and its frequency will be evaluated by comparing near and far transfer observed at the three training groups.

Ethics and dissemination: The study is conducted with ethics approval of the national ethical committee CPP Sud Méditerranée III (Nr. 2019-A00458-49) and of the National Commission for Information Technology and Liberties (Nr. 919217). Written and signed informed consent is obtained from each participant. The results of the study will be disseminated in the form of oral communications or posters in international conferences (e.g., Alzheimer's Association International Conference) and published in a scientific journal in the field (e.g., Journal of Alzheimer's Disease).

Trial registration number: ClinicalTrials.gov identifier (NCT04010175).

Keywords: prodromal to moderate Alzheimer's disease, computer-based cognitive training, at home cognitive training, cognitive benefits, quality of life improvement

Strengths and limitations of the study

► This study will provide information on the short- and long-term effects of remote computer-based cognitive training in addition to regular training in SLT office for Alzheimer's patients.

► This study will shed light on the optimal cognitive training frequency to be administered.

► This study will evaluate the adherence to the computerized program at home in comparison with the trainings carried out exclusively in the SLT office, knowing that this factor is likely to be favorable to the adherence taking into account the reduction of travel and the training in a familiar environment.

► The limitation of the present study is that it will not control the familiarity of the Alzheimer's disease patients with the computer tool, nor their degree of autonomy in accomplishing the training at home on their own.

INTRODUCTION

Considering increasing occurrence of neurodegenerative disorders in the elderly, such as Alzheimer's disease (AD), and in the absence of effective drug treatment, usage of cognitive training seems to be a promising alternative in healthy and pathological aging for improving cognitive functioning [1-3] and quality of life [4-5]. For some researchers cognitive training also constitutes an added value to drug treatment, as it was observed to amplify the expression of drug effects [6].

The efficacy of cognitive training in patients with AD is still under the debate [8], especially concerning the best methodological approaches to be applied to optimize the training outcomes [9-10], including training feasibility, patient's commitment, and motivation. The computer-based cognitive training (CBCT) seems to have several advantages because it provides wide variety of well-calibrated exercises and allows for example to easily adapt their difficulty to each patient [11]. The CBCT short- and long-term benefits was first shown in healthy elderly [7,12,13], but has also been proven in patients with AD and MCI [14-18].

Several studies have highlighted the importance of some essential criteria for successful training, whatever its type [19, 15, 20]. Globally, the studies recommend early intervention with sessions between 30 minutes and 1 hour and session's frequency set at several times a week [9-10, 21]. Such a design is supposed to maintain strong commitment and motivation throughout the training, indispensable for its efficiency. However, these recommendations face some important problems that render their application difficult. First, few people are concerned about small changes in performance, the majority will only consult when symptoms become more pronounced, which prevents from early intervention suggested by several authors [21-25]. Second, patients' involvement in high frequency cognitive training protocols faces several difficulties, most importantly, frequent travels between home and speech-language pathologist's office (SPL). As the disease progresses, autonomy is compromised, and the need of a caregiver's help is a supplemental difficulty. In addition, the changing seasons lead to many health problems that hinder the training and often lead to interruptions. One way of circumventing these problems would be to propose a CBCT including some sessions at home [26,17].

The main objective of the present study is to examine the short- and long-term benefits of CBCT realized at home as a complement to in-office CBCT in mild to moderate Alzheimer's disease patients. The secondary objective is to evaluate the best frequency of the at home training. To do so, we administer computer-based cognitive training for 4 months under three conditions: (1) in SPL's office one-time per week, (2) in SPL's office one time per week plus one time at home, and (3) in SPL's office one time per week plus three times at home.

Method

1. Design

This is an experimental study with minimal risks, with 3 parallel groups, namely in SLT's office only training group (REG – regular group), in SPL's office plus one session per week at home (MFG - moderate frequency group) and in SPL's office plus three session per week at home (HFG – high frequency group). The inclusion of patients will be done for 2 years, starting from the 1st September 2019 and ending 1st September 2021. For each participant, the inclusion period is approximately 8 months. During this period, participants cannot be included in other protocols that are susceptible to influence their cognitive or emotional functions. The total duration of the study is 32 months. All inclusions and testing will be realized in SLT offices. The training will be done in SLT offices and at patients' homes (see Figure 1 for a study design).

This study obtained the authorization of the national ethical committee CPP Sud Méditerranée III (Nr. 2019-A00458-49, version 5 from 18/11/2019) and of the National Commission for Information Technology and Liberties (Nr. 919217) and was registered on clinicaltrials.gov (NCT04010175).

Insert Figure 1 here

2. Participants

This study concerns people over 60 years of age with a diagnosis of prodromal to moderate Alzheimer's disease. To recruit participants, we contacted SLTs subscribers to SBT's Happyneuron Pro digital tools through the SBT Human(s) Matter company network. They first answered a questionnaire in order to identify SLTs practicing with AD patients. These SLT received an invitation letter for participation to our study. Finally, 27 SLTs from different parts of France joined the study and become clinical investigation centers (CIS). A full list of these SLTs can be obtained from the Department of Clinical Research and Innovation of the Hospices Civils of Lyon[1]. Each SLT oversees presenting the study in his or her office to patients whose profile match our inclusion criteria. The interested patients will receive the information and consent leaflets. During the next visit they will be asked if he/she wished to participate

[1] Direction de la Recherche Clinique, Hospice Civil de Lyon
3, quai des Célestins, 69229 Lyon Cedex 2

to the study, and if so the informed consent will be signed. Thus, the patients are included by the SLTs who also sign a informed consent after the neurologist's validation, the Principal Investigator of this study. Patients are informed that during the study they cannot take part in any other study that could potentially have an effect on their cognitive functions.

2.1 Eligibility

The eligibility criteria are presented in Box 1.

Insert Box 1 here

2.2 Withdrawal Criteria

Each patient is free to withdraw from the study at any time without giving the reasons, by simply informing one of the investigators. If consent is withdrawn, the data collected up to the date of withdrawal will be analyzed.

3. Randomization and Anonymization Method

To avoid any unequal treatment of patients in the same SLT, we decided to randomize SLTs' offices to different training groups, instead of randomizing patients. Thus, each office will be assigned to one of training group and all patients included in this SLT office will follow the same training procedure (REG, MFG or HFG). The offices will be assigned to each group in a balanced way in terms of socio-demographic considerations, depending on their geographical location. It will be done by a Head of Research & Development department in SBT before the study beginning. If, despite randomization, an imbalance occurs within groups due to inter-individual differences such as age, gender, education and disease severity, these factors would be considered as covariant in results analysis.

Each patient will receive an anonymization number composed, in order, of the number of the investigating center, the inclusion number for this center and the patient's initials. The SLT will keep the table of correspondence between this number and the first and last name, as well as the address and telephone number for all patients included in his/her center.

4. Procedure

Our study follows a conventional protocol used to evaluate the cognitive and psychological benefits resulting from cognitive training (for a review, [42]) (see Figure 2 and Table 1 for details).

Insert Figure 2 and Table 1 here

5. Primary measures of training benefits

Our primary measures, performed by SLTs, are patient's scores on neuropsychological tests, questionnaires, and experimental tasks performed in the three time-points (T0, T1, and T2). The choice of these measures was made according to the trained cognitive functions and the cognitive (working memory, executive functions) and psychological (self-esteem, motivation, psychological state - depression/anxiety, assessment of quality of life) domains for which training benefits are expected. These evaluations enable us to first determine the baseline level of patient's cognitive capacities and his or her emotional and motivational state and second to measure the training benefice by comparing the pre-training results (T0) with those obtained immediately after the end of the training (T1) and 3 month later (T2).

5.1 Neuropsychological tests

Verbal Fluency [27]

The overall objective of the fluency test is to evaluate executive functions by accessing patient's capacity to access their lexical repertoire according to a given letter or a semantic category.

TMT A/B [28]

Trail Making Test consists of two parts. Part A measure processing speed – the patient must connect in ascending order the 25 numbers randomly distributed in circles on the A4 page. Part B measure cognitive flexibility – the patient must perform the same task as in part A while alternating between numbers and letters (i.e., 1-A-2-B-3-C, etc.).

Logical Memory [29]

Logical Memory I and II are subtests of the *MEM Wechsler IV*. Each correctly recalled detail out of 25 details per story is scored 1 point, giving the maximum raw score of 50 points for two stories. Logical

Memory II is a delayed condition of Logical Memory I. The test ends with recognition, in which patient must answer a series of questions concerning each story.

MMSE [30]

The Mini Mental State Examination (MMSE) is a commonly used test for screening general cognitive impairment. The maximum MMSE score is 30 points.

Digit Span [29]

Two types of span are used, forward and backward to measure respectively short-term and working memory. For both span the test ends if the participant fails to repeat two consecutive series. The maximum score is 48.

5.2 Questionnaires

Geriatric Depression Scale (GDS) 30 items [31]

GDS is 30 items**,** self-reported scale that uses "Yes/No" responses. It is used to detect the symptoms of depression in older adults. Scores of 0-4 are considered normal, 5-8 indicate mild depression; 9-11 indicate moderate depression; and 12-15 indicate severe depression.

Questionnaire of Cognitive Complaint [32]

It is a yes/no 10 questions survey targeting memory, language, orientation, and behavior, enabling clinicians to distinguish between a benign cognitive complaint and an at-risk complaint.

Instrumental Activities of Daily Living (IADL) [33]

Eight areas of daily functioning are measured with IADL scale, with a score ranging from 0 (dependent) to 8 (independent) for women and from 0 to 5 for men.

Pittsburg Sleep Quality Index (PSQI) [34]

It is used to measure quality and sleep cycles in older adults by assessing seven sleep domains. It is self-reported measure giving a global score ranging from 0 (no difficulties) to 21 (severe difficulties), with the score higher than 5 reflecting disturbance of sleep and its quality.

SF 12 [35]

It is a self-reported 12 questions survey assessing the quality of life and more specifically the incidence of health condition on daily living by exploring 8 areas. Two scores are calculated – a mental component score (MCS-12) and a physical component score (PCS-12).

Motivation scale for older adults [36]

This scale measures intrinsic motivation, extrinsic self-determined and non-self-determined motivation and amotivation in different life contexts. There are 12 motivational statements per life context. Each of the statements is evaluated on a scale of 1 to 7 points.

5.3 Experimental Tasks

Four experimental tasks were constructed to measure near transfer of the effects of the training on executive functions and memory, the cognitive functions targeted by the training.

Stop Signal [37]

This task evaluates inhibition capacities. The participant is asked to give a response to the presentation of a target stimulus (Go signal) and to prevent this response when the stimulus is followed or preceded by a beep (Stop signal). The task includes two phases. The mean reaction time for each participant is calculated to be used in a second phase as a reference time for auditory signal presentation. In total, there are 96 trails. The trails are presented in randomized manner. The auditory signal presentation is adaptive. The first signal is presented after the stimulus presentation at reference time calculated in the phase 1. Each following signal is presented depending on the participant's capacity to withhold his/her response. If the participant succeeds, the time is increased by 10ms, if the participant fails the time is decreased by 10ms.

Letter and number pairs [38]

This task is used to evaluate mental flexibility. The participant sees 4 blocks of 48 letter-number pairs giving in total 192 trials presented in aleatory manner. Each pair appears for 350 ms on a computer screen, either in a square located in the upper part of the screen or in a square located in the lower part of the screen. The participant is asked to make a parity judgement if the pair appears at the upper part of the screen, and to make consonant/vowel judgement if it appears at the lower part of the screen. Reaction time and accuracy are recorded.

Up-dating span [38]

This task is used to evaluate up-dating in working memory. The series of letters appear on a computer screen, the participant is asked to memorize the last three presented letters, without knowing the length of the series. The series are presented in random order. Reaction time and accuracy are recorded.

Operation reading letters span [39]

This task is used to evaluate working memory. It consists of 8 series of 2 to 5 letters. The letters are separated by a presentation of one, two or three operands composed of one or two digits. The participant is asked to memorize each series of letters while reading aloud between each letter the operations and their results. In the end of the series the participant is asked to recall in serial order the letters.

6. Computer-based cognitive training

Training will be done for each participant over a period of 4 months on the PC computer with the Happyneuron Pro software (https://www.scientificbraintrainingpro.fr). Patients will realize the training as indicated in Design section, page 5. In the beginning of each session SLT will ask participant to report any event that have occurred during the week and could in any way disturb his/her participation to the training. These events will be reported in the EON. A 4-months training period is justified by the fact that we wish to evaluate the benefits of a fairly short period that would be less prone to drop out and whose duration is sufficient, according to the literature, to produce benefits. We choose the training tool, Happyneuron Pro, because it is a well-known product for cognitive remediation and frequently used by the SLTs in France, and in particular by SLTs participating to our study.

Each training session of 45 minutes includes 10 exercises of different durations, but not exceeding 4 minutes (see Table 2 for details). The training program automatically stops after 45 minutes, even if the patient has not completed the 10 exercises scheduled for the session. The training is adaptable from session to session. Thus each session begins on the exercise and the level on which the previous session stopped. Each exercise has 9 levels of difficulty and each level is displayed at least twice. This is because the criterion for passing to a higher level of difficulty is to successfully execute the current level two consecutive times.

The training targets the following cognitive functions: working and short-term memory, executive functions, visuo-spatial capacities and processing speed.

Insert Table 2 here

7. Equipment and programming

The SLT's office and patient's personal computers are the only equipment used to run our protocol. All questionnaires and neuropsychological tests (except TMT and Figure from MMSE) were digitalized on Typeform. Experimental tasks were designed and programmed on the Open Sesame free access Software (Version 3.2.5). Thus, this software was installed on the SLT's computers. The training sessions were programmed on Happyneuron Pro Platform https://www.scientificbraintrainingpro.fr/

8. Study Management

8.1 General management

Each SLT participating in the study was provided an appropriate training to use all tools necessary for conducting the protocol. The training was delivered during videoconferences in small groups or individually and completed by e-mail exchanges and video tutorials, digital user guide, and power point presentations.

Each SLT has two personal spaces secured by password, one on the Happyneuron Pro platform to manage the trainings and another one on the Ennov Clinical containing the electronic observation notebooks (EON) of the patients to store all clinical information and results of neuropsychological tests and experimental tasks for each patient. It is hosted on the secured platform of Hospices Civils de Lyon (HCL). These personal areas are supervised by principal investigator, junior investigator of this study, and a clinical research assistant of HCL.

The workspace on Happyneuron Pro platform is used to create the training area for each included patient and to specify the frequency per week and the days of training sessions, depending on the training group. Once the patient's space is created and the sessions scheduled, the patient receives a link by email on the scheduled days and all he must do to access the training, is to click on the link.

The monitoring of the study is done by the Department of Clinical Research and Innovation of the Hospices Civils of Lyon[2]. A designed clinical research assistant is in charge of the monitoring that includes :

- a study start-up visit to the coordinating center and the inclusion centers,
- a mid-term visit
- a closing visit

During mid-term and closing visits the verification of consent forms and EON will be done.

The coordinating center is composed of the three investigators (principal, senior and junior investigator) who designed the protocol and will be in charge of verification of inclusion/exclusion criteria before patients inclusion to the study and in the analysis of the data. These investigators are not involved in data collection.

8.2. Data management and storage

[2] HCL's identification code for the study 69HCL18_0881

The performance on the neuropsychological tests conducted via Typeform are automatically recorded. When they are completed an email with the patients' scores is automatically sent to the investigator and the SLT, and patients scores can be extracted from Typeform on Excel. In the end the SLT enters the scores of interests into the patient's EON.

Performances on the experimental tasks are recorded on the SLT's office computer and then the scores of interests are entered into the patient's EON.

The training results for each session are automatically recorded on a secure server hosted by a health data host. There is no transit between servers, no storage of data on the patient computer. SLTs have the possibility to monitor the trainings remotely: this is possible by accessing the patient's space, enabling the SLTs to check if the training has been regularly carried out and to follow patients' progression. If necessary, the SLT can also access the results online.

All the data entered in EON are accessible during the period of inclusion and after the end of the study to the clinical research assistant in charge of the study monitoring and to the three investigators in charge of this study and who do not take part in the data collection. The data extraction and analysis are allowed at two points of the study, mid-term and the end of inclusion period. The final trail dataset that will be used for statistical analysis will be accessible to the three investigators in charge of this study.

9. Statistical considerations

9.1 Estimation of samples size

The sample size per training group was estimated on previous protocols and literature reviews [9, 40] which show that the number of patients included in protocols varies between 15 and 150 per group. Taking into account the data of previous studies and expected size effect, we decided to include 55 patients per group. Indeed, the size of each group was estimated to be 45, assuming a small effect of the intervention (Cohen's d = 0.40), with a repeated measures factor Time of assessment (pre-training, immediate post-training, long term post-training) and an independent measures factor of Group (MFG, HFG, REG) to reach a power of 0.8 with an alpha at 0.05. We have estimated a 10% dropout rate by the participants. Thus, we have estimated the inclusion of 50 patients per group. In addition, to consider the cluster randomization we have estimated that we should increase our sample by 10%, bringing the number of patients per group to 55. This number is compatible with our capacity of patients' recruitment.

9.2 Statistical methods description

Linear models are considered for all behavioral measures collected with one random intercept per patient and one per practice. The analysis will concern independent measures factor Group with three modalities (MFG, HFG, REG) and repeated measures factor Time with three modalities (T0 - pre-training, T1 - post-training, T2 - long term monitoring) and the interaction between these two factors. Level of significance is fixed to 0.05.

The interim analyses are also planned, using the same models as described above, at three time points: 1 - after inclusion of 15 patients in each group, 2 - after inclusion of 30 patients in each group, and 3 - after inclusion of 40 patients in each group. We decided to perform interim analyses to see if trends would emerge on smaller samples than those estimated by the power analysis to be necessary to obtain a training effect. These analyses are not intended to modify the protocol or the planned inclusions.

Statistical analyses will be carried out using STATISTICA software.

10. Risks and benefits

There is no particular risk for patients to participate in this study. The only drawbacks could be computer-related fatigue, especially for patients included in HFG.

The major personal benefit for patients would be an improvement in their cognitive and emotional state or a slowing of the cognitive deficit progression. The secondary benefit could be the improvement of their quality of life.

There is also a collective benefit since if the results of this study confirm our hypothesis, we could give recommendations concerning at home training.

11. Ethics and dissemination

The study is conducted with ethics approval of the national ethical committee CPP Sud Méditerranée III (Nr. 2019-A00458-49) and of the National Commission for Information Technology and Liberties (Nr. 919217). Any modification to the study design has to be communicated to the clinical research assistant and if necessary a request for amendment must be addressed to the national ethical committee who has delivered the approval for the study. The results of the study will be disseminated in the form of oral communications or posters in international scientific conferences and seminars for healthcare professionals (e.g., Alzheimer's Association International Conference, Union Nationale pour

le Dévelopment de la Recherche et de l'Evaluation en Orthophonie) and published in a scientific journal in the field (e.g., Journal of Alzheimer's Disease). The communications are allowed after the first statistical analyses planed at the mid-time period of inclusion.

12. Patient and Public Involvement

Patients and public were not involved in any way in a conception of this study.

13. Significance

In a general way this study will contribute to the knowledge of cognitive training effects on cognition in patients with Alzheimer's disease in the prodromal to moderate stages. The comparison of results obtained for neuropsychological tests, questionnaires, and experimental tasks by REG patients with those obtained by MFG patients will inform about the effects of at home cognitive training done as a complement to training performed in SLT office. This will provide clear indications as about the usefulness of this type of cognitive training program for AD patients. Comparison of results obtained by MFG patients with those obtained by HFG patients will provide indications regarding the best necessary frequency of the training sessions.

Beyond the benefits of cognitive training on the cognition of patients with AD, and the importance of trying to determine the best frequency to obtain the optimal effects, other issues, that are independent of the cognitive training program, may impact its success if they are not carefully considered. The AD has an important impact on autonomy, emotional balance, and motivation, very often linked to self-esteem [19-21]. Thus, it seems important, when designing cognitive training protocols for AD patients, to consider psychological, environmental and autonomy factors for a more optimal cognitive training plan, that seeks the well-being of the individual as a whole [21,41]. Through questionnaires administered in our protocol [31-36], we hope to shed light on the emotional benefits of training and answer questions regarding the commitment and adherence to the program by AD patients, as well as to provide a more informed opinion on the importance of seeking assistance from a third party. Understanding whether the same issues of autonomy in training are involved for patients with mild and moderate AD will allow us to elaborate more precise computer-based home training protocols for different patient's profile. These protocols should take into consideration the cognitive decline severity that may affect autonomy in training as cognitive impairment increases. Such considerations will bring us to foresee solutions when it comes to training performed at home for those who are less autonomous.

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Authors Contribution

All the authors were involved in the study design and critically reviewed and approved the final manuscript. SD drafted the manuscript.

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Competing interests' statement

The authors declare that they have no known competing financial interest or personal relationship that could have appeared to influence the work reported in this paper.

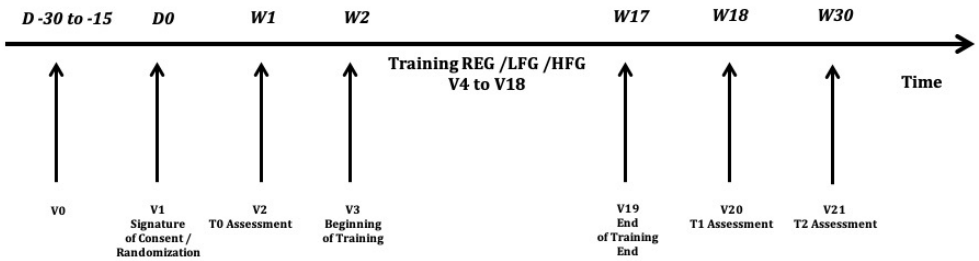

Figure 1

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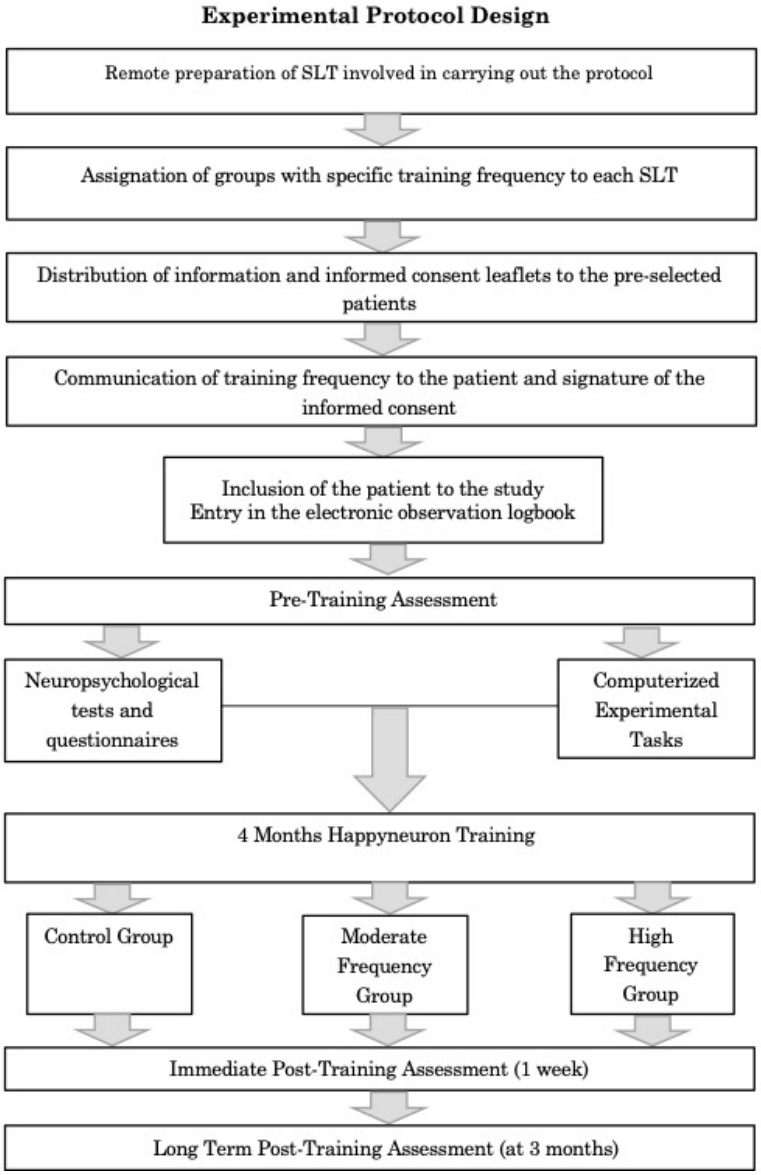


Figure 2

190x271mm (72 x 72 DPI)

Boxes and Tables

Box 1. Eligibility criteria
Inclusion criteria: 1. Age ≥ 60 years 2. Native French speaker 3. Diagnosis of Alzheimer's disease according to the DSM V criteria 4. Mild to moderate cognitive impairment as stage of disease progression (Mini-Mental State Examination >15/30) 5. Unchanged psychotropic treatment in the month prior to inclusion 6. Signed informed consent for a participation to the study (personally or by a legal representative)
Exclusion criteria: 1. Uncorrected vision or hearing impairments 2. Motor dysfunction symptoms that could prevent the tests from being carried out 3. Not having a computer preventing cognitive training at home 4. Receiving SLT care for more than 3 months 5. Refusal to participate in the study 6. Being under guardianship or curatorship

Table 1. The main steps of the protocol process with the timetable.

Steps	V0 Pre-inclusion	V1 Inclusion	V2 Assessment T0	V3 à V19 Training	V20 Assessment T1	V21 Assessment T2
Time / Actions	D-30 à D-15	J0	S1	S2-S17	S18	S30
Allocation	X					
Eligibility screen	X					
Study presentation to the patient	X					
Signature of the informed consent		X				
Assessments (Neuropsychological tests, questionnaires and experimental tasks)			X		X	X
Cognitive training						
Group REG				X		
Group HFG				X		
Group MFG				X		
Collection of adverse events			X	X	X	X

Table 2. Exercises included in cognitive training and cognitive capacity targeted by the exercise.

Game type	Cognitive capacity targeted by the exercise
1- Tower of Hanoi	- Problem solving
2- Put some order in these accounts	- Visuospatial exploration - Attention and numerical processing
3- Bird songs	- Auditory memory - Memorizing strategies
4- Objects, where are you?	- Visuospatial memory - Binding capacities
5- Find your way back.	- Visual short-term memory - Working memory
6- Blazon Game	- Visual memory - Attention - Visuospatial perception
7- Waiter please	- Verbal memory - Visual memory - Mental rotation ability
8- Conduct the investigation	- Lexical comprehension - Categorization skills
9- It is up to you to count	- Working memory - Mental arithmetic
10- You have got a message	- Verbal-auditory memory

COMITE DE PROTECTION DES PERSONNES
SUD MEDITERRANEE III

Président: J-Y. LEFRANT Vice-Président: A-M. JOUBERT

Référence CPP à rappeler:	2019.04.08 ter_ 19.03.08.44936	Nîmes, le:	09 Décembre 2019
Lors de sa séance du:	05 décembre 2019	Présidée par Mme ou M:	J-Y. LEFRANT

En présence des membres suivants: Mmes et MM:		Membres titulaires		Membres suppléants	
1er Collège	Personnes qualifiées en recherche biomédicale	X	J-Y. LEFRANT S. DROUPY D. MOTTET	X X	C. LECHICHE R. DE TAYRAC L. GONTHIER-MAURIN
	Compétents en biostatistique/épidémiologie		C. DEMATTEI	X	S. BASTIDE
	Médecins généralistes		P. SERAYET	X	C. GRAS-AYGON
	Pharmaciens hospitaliers		A. MOURGUES	X	G. LEGUELINEL
	Infirmiers	X	G. BAVILLE		A. GIRON
2e Collège	Compétents en questions éthiques	X	C. BERHAULT	X	V. ANTOINE
	Psychologues	X	L. HERITIER		C. AYELA
	Travailleurs sociaux		P. BERTAUDON		
	Compétents en matière juridique	X	E. TOULOUSE-MULLER C. ROLLAND		M. GRIT
	Représentants d'associations agréées de malades et usagers du système de santé	X	A-M. JOUBERT Y. PRIOUX	X	A. MENSUELLE-FERRARI
Personnes cooptées	Pédiatre				
	Spécialiste pour défaut de consentement				

Les membres suivants s'étant retirés: Mmes et MM:

Le comité de protection des personnes Sud Méditerranée III a examiné les informations relatives à un projet référencé localement sous le numéro ci-dessus, et identifié par le numéro ci-dessous, relatif à:		
		Recherche interventionnelle de type 1
	X	Recherche interventionnelle de type 2
		Recherche non interventionnelle de type 3
		Utilisation d'éléments et produits du corps humain
		Collection d'échantillons biologiques

Numéro d'enregistrement:	EudraCT		ANSM 2019-A00458-49

Intitulé du projet:	"MA-EIAD : Prise en charge de déficits cognitifs chez des patients atteints de la maladie d'Alzheimer au stade prodromal à modéré : Quels apports d'un entraînement informatisé à distance ?"
Promoteur	HOSPICES CIVILS DE LYON
Investigateur principal ou coordonnateur:	DR. CROISILE
Lieu de recherche (si soumis à autorisation):	

Au titre d'une demande d'avis concernant:		Projet initial	Dans le cadre de:	X	Première soumission
	X	Modification substantielle N° 1			Nouvelle soumission d'un projet modifié en réponse aux observations du comité

Date de réception du projet visé	19 novembre 2019

X	Le comité, ayant examiné ou réexaminé le projet soumis, exprime en séance plénière l'avis ci-contre:	X	Favorable
			Défavorable
	Le projet ayant fait l'objet de réserves mineures lors de la délibération initiale, et celles-ci ayant été prises en compte, le comité exprime ce jour l'avis ci-contre:		Différé P2P (**sans 2ème passage**) 2P (**2ème passage**) Eclaircissements des réponses apportées

Date de prise d'effet du présent avis:	05 décembre 2019

Le président:	X	Le vice-président:		Le président de séance:	

Adresser la correspondance à : CPP SUD-MEDITERRANEE III, UFR MEDECINE 186, chemin du Carreau de Lanes CS 83023
30908 NIMES Cedex 2
Secrétariat : Mme CABRERA Téléphone/Fax : 04 66 02 81 55
e-mail : cpp.sudmediterranee3@gmail.com

COMITE DE PROTECTION DES PERSONNES
SUD MEDITERRANEE III

Président: J-Y. LEFRANT Vice-Président: A-M. JOUBERT

Référence CPP à rappeler:	2019.04.08 ter _ 19.03.08.44936

Le présent avis concerne spécifiquement les documents suivants:		Version n° :	En date du:
X	Courrier de demande		19 novembre 2019
X	Courrier de demande de modification substantielle		19 novembre 2019
X	Formulaire de demande		19 novembre 2019
X	Demande d'amendement au protocole		05 novembre 2019
X	Tableau comparatif des modifications		
X	Protocole	4	18 novembre 2019
X	Résumé protocole	5	18 novembre 2019
X	Note d'information et consentement destiné aux patients	4	18 novembre 2019
X	Liste investigateur	2	18 novembre 2019
X	CV du ou des investigateurs		

REMARQUES

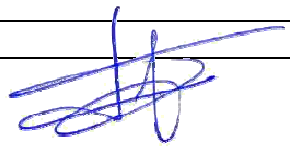
(1) Le comité prend en considération pour sa décision les conditions de validité de la recherche au regard de la protection des personnes, notamment l'information des participants avant et pendant la durée de la recherche y compris l'adéquation, l'exhaustivité et l'intelligibilité des informations écrites, les modalités de recueil de leur consentement, les indemnités éventuellement dues, la pertinence générale du projet et l'adéquation entre les objectifs poursuivis et les moyens mis en œuvre, ainsi que la qualification du ou des investigateurs.

(2) Quel que soit l'avis du Comité, il ne dégage pas le promoteur de sa responsabilité.

(3) Conformément à la réglementation, tout avis est transmis à l'autorité compétente et, en cas d'avis défavorable, aux autres comités.

(4) En cas d'avis différé, le promoteur est invité à transmettre au comité dans les meilleurs délais les informations complémentaires demandées et/ou le projet modifié répondant aux réserves exprimées. Il peut demander, ainsi que l'investigateur principal, à être entendu par le comité.

MOTIVATION DE L'AVIS DU COMITE



Adresser la correspondance à : CPP SUD-MEDITERRANEE III, UFR MEDECINE 186, chemin du Carreau de Lanes CS 83021
30908 NIMES Cedex 2
Secrétariat : Mme CABRERA Téléphone/Fax : 04 66 02 81 55
e-mail : cpp.sudmediterranee3@gmail.com

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	7
Protocol version	#3	Date and version identifier	5
Funding	#4	Sources and types of financial, material, and other support	19
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1;19

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	n/a
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	6

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-9
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n/a

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5-6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7-9; 11
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	13
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	13
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	13
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13-14
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	19
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Study design and protocol of a low to high intensity computer-based cognitive training at home in supplement to standard care in patients with AD

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-050993.R1
Article Type:	Protocol
Date Submitted by the Author:	23-Dec-2021
Complete List of Authors:	Dimachki, Samar; Université Lyon 2, Laboratoire d'Etude des Mécanismes Cognitifs Tarpin-Bernard, Franck; Universite Grenoble Alpes UFR Informatique Mathématiques et Mathématiques Appliquées de Grenoble, Laboratoire d'informatique de Grenoble Croisile, Bernard; Hospices Civils de Lyon, Neurology Hospital - Neuropsychology Department Chainay, Hanna; Universite Lumiere Lyon 2, EMC Laboratory - (Etudes des Mécanismes Cognitifs)
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Geriatric medicine, Neurology, Mental health, Medical management, Palliative care
Keywords:	GERIATRIC MEDICINE, Dementia < NEUROLOGY, MENTAL HEALTH, PREVENTIVE MEDICINE, Delirium & cognitive disorders < PSYCHIATRY, COMPLEMENTARY MEDICINE

Study design and protocol of a low to high intensity computer-based cognitive training at home in supplement to standard care in patients with AD

Samar Dimachki[1,3], Franck Tarpin-Bernard2[3], Bernard Croisile[2,3] & Hanna Chainay[1]

[1] Laboratoire d'Étude des Mécanismes Cognitifs, Université Lyon 2, Bron, France

[2] Service de Neuropsychologie, Centre Mémoire de Ressource et de Recherche de Lyon, Hôpital Neurologique, Bron, France

[3] Scientific Brain Training SA, Lyon, France

samar.dimachki@univ-lyon2.fr

f.tarpin@sbt-human.com

bernard.croisile@wanadoo.fr

hanna.chainay@univ-lyon2.fr

Corresponding author: Samar Dimachki

Université Lyon 2

Laboratoire d'Étude des Mécanismes Cognitifs

5 avenue Pierre Mendès France

69676 Bron, France

E-mail : samar.dimachki@univ-lyon2.fr

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Abstract

Introduction: Recent studies on cognitive training in patients with Alzheimer's disease (AD) showed positive long-term effects on cognition and daily living, suggesting remote computer-based programs to increase training sessions while reducing patient's travelling. The aim of this study is to examine short- and long-term benefits of computer-based cognitive training at home in mild to moderate patients with AD, as a complement to the training in speech and language therapist (SLT) offices. The secondary purpose is to study training frequency required to obtain noticeable effects.

Methods and analysis: This is a national multi-center study, conducted in SLT offices. The patients follow training in one of three conditions: once a week in SLT office only (regular condition) and once a week in SLT office plus one or three times per week at home. The trainings' content in SLT office and at home are identical. For all three groups near and far transfer will be compared to evaluate training frequency's effect. Our primary outcome is executive and working memory scores in experimental tasks, and the secondary is neuropsychological tests and questionnaires' scores. Linear models' analysis are considered for all measures with a random intercept for patients and another for per practice. The fixed effects will be: three modality Groups and Time, repeated measures, (T0- pre-training, T1 - post-training, T2 - long-term follow-up) and the interaction pairs.

Ethics and dissemination: The study got ethics approval of the national ethical committee CPP Sud Méditerranée III (Nr. 2019-A00458-49) and of the National Commission for Information Technology and Liberties (Nr. 919217). Informed consent is obtained from each participant. Results will be disseminated in oral communications or posters in international conferences and published in scientific journals.

Trial registration number: ClinicalTrials.gov identifier (NCT04010175).

Keywords: Alzheimer's disease, MCI, computer-based cognitive training, at home cognitive training, cognitive benefits, quality of life

Strengths and limitations of the study

► This study will provide information on the short- and long-term effects of remote computer-based cognitive training in addition to regular training in SLT office for patients with AD.

► This study will shed light on the optimal cognitive training frequency to be administered.

► This study will evaluate the adherence to the computerized program at home in comparison with the trainings carried out exclusively in the SLT office, knowing that this factor is likely to be favorable to the adherence taking into account the reduction of travel and the training in a familiar environment.

► The limitation of the present study is that it will not control the familiarity of the Alzheimer's disease patients with the computer tool, nor their degree of autonomy in accomplishing the training at home on their own.

INTRODUCTION

Considering increasing occurrence of neurodegenerative disorders in the elderly, such as Alzheimer's disease (AD), and in the absence of effective drug treatment, usage of cognitive training seems to be a promising alternative in healthy and pathological aging for improving cognitive functioning [1-3] and quality of life [4-5]. For some researchers cognitive training also constitutes an added value to drug treatment, as it was observed to amplify the expression of drug effects [6].

The efficacy of cognitive training in patients with AD is still under the debate [7], especially concerning the best methodological approaches to be applied to optimize the training outcomes [8-9], including training feasibility, patient's commitment, and motivation. The computer-based cognitive training (CBCT) seems to have several advantages because it provides wide variety of well-calibrated exercises and allows for example to easily adapt their difficulty to each patient [10]. The CBCT short- and long-term benefits were first shown in healthy elderly [11,12], but have also been proven in patients with AD and MCI [13-17].

Several studies have highlighted the importance of some essential criteria for successful training, whatever its type [18, 14, 19]. Globally, the studies recommend early intervention with sessions between 30 minutes and 1 hour and session's frequency set at several times a week [8-9, 20]. Such a design is supposed to maintain strong commitment and motivation throughout the training, indispensable for its efficiency. However, these recommendations face some important problems that render their application difficult. First, few people are concerned about small changes in performance, the majority will only consult when symptoms become more pronounced, which prevents from early intervention suggested by several authors [20-24]. Second, patients' involvement in high frequency cognitive training protocols faces several difficulties, most importantly, frequent travels between home and speech-language pathologist's office (SPL). As the disease progresses, autonomy is compromised, and the need of a caregiver's help is a supplemental difficulty. In addition, the changing seasons lead to many health problems that hinder the training and often lead to interruptions. One way of circumventing these problems would be to propose a CBCT including some sessions at home [25,16]. Our main hypothesis is that remote cognitive training using computer-based programs is an effective way to increase the cognitive and psychological benefits of training as an outcome of training. We also hypothesized that more frequent training (e.g., several times per week) should bring more important benefits than training performed once a week.

The main objective of the present study is to examine the short- and long-term benefits of CBCT realized at home as a complement to in-office CBCT in mild to moderate patients with AD. The

secondary objective is to evaluate the best frequency of the at home training. To do so, we administer computer-based cognitive training for 4 months under three conditions: (1) in SPL's office one-time per week, (2) in SPL's office one time per week plus one time at home, and (3) in SPL's office one time per week plus three times at home.

Method

1. Design

This is an experimental study with minimal risks, with 3 parallel groups, namely in SLT's office only training group (REG – regular group), in SLT's office plus one session per week at home (MFG - moderate frequency group) and in SLT's office plus three session per week at home (HFG – high frequency group). The inclusion of patients will be done for 2 years, starting from the 1st September 2019 and ending 1st September 2021. For each participant, the inclusion period is approximately 8 months. During this period, participants cannot be included in other protocols that are susceptible to influence their cognitive or emotional functions. The patients and their caregivers are informed about this point before signing the informed consent and the SLTs are asked to monitor this throughout the protocol. The total duration of the study is 32 months. All inclusions and testing will be realized in SLT offices. The training will be done in SLT offices and at patients' homes (see Figure 1 for a study design). The content of the trainings in SLT office and at home are identical.

This study obtained the authorization of the national ethical committee CPP Sud Méditerranée III (Nr. 2019-A00458-49, version 5 from 18/11/2019) and of the National Commission for Information Technology and Liberties (Nr. 919217) and was registered on clinicaltrials.gov (NCT04010175).

FIGURE 1

2. Participants

This study concerns people over 60 years of age with a diagnosis of prodromal to moderate Alzheimer's disease. To recruit participants, we contacted SLTs subscribers to SBT's Happyneuron Pro digital tools through the SBT Human(s) Matter company network. They first answered a questionnaire in order to identify SLTs practicing with patients with AD. These SLT received an invitation letter for participation to our study. Finally, 27 SLTs from different parts of France joined the study and become clinical investigation centers (CIS). A full list of these SLTs can be obtained from the Department of Clinical Research and Innovation of the Hospices Civils of Lyon[1]. Each SLT oversees presenting the study in his or her office to patients whose profile match our inclusion criteria. The interested patients will receive the information and consent leaflets. During the next visit they will be asked if he/she wished to participate to the study, and if so, the informed consent will be signed. Thus, the patients are included by the SLTs who also sign an informed consent after the neurologist's validation, the Principal Investigator of this study. Patients are informed that during the study they cannot take part in any other study that could potentially have an effect on their cognitive functions.

2.1 Eligibility

The eligibility criteria are presented in Box 1.

Box 1. Eligibility criteria
Inclusion criteria: 1. Age ≥ 60 years 2. Native French speaker 3. Diagnosis of Alzheimer's disease according to the DSM V criteria 4. Mild to moderate cognitive impairment as stage of disease progression (Mini-Mental State Examination >15/30) 5. Unchanged psychotropic treatment in the month prior to inclusion 6. Signed informed consent for a participation to the study (personally or by a legal representative)
Exclusion criteria: 1. Uncorrected vision or hearing impairments 2. Motor dysfunction symptoms that could prevent the tests from being carried out 3. Not having a computer preventing cognitive training at home 4. Receiving SLT care for more than 3 months 5. Refusal to participate in the study 6. Being under guardianship or curatorship

[1] Direction de la Recherche Clinique, Hospice Civil de Lyon
3, quai des Célestins, 69229 Lyon Cedex 2

2.2 Withdrawal Criteria

Each patient is free to withdraw from the study at any time without giving the reasons, by simply informing one of the investigators. If consent is withdrawn, the data collected up to the date of withdrawal will be analyzed.

3. Randomization and Pseudonymization Method

To avoid any unequal treatment of patients in the same SLT, we decided to randomize SLTs' offices to different training groups, instead of randomizing patients. Thus, each office will be assigned to one of training group and all patients included in this SLT office will follow the same training procedure (REG, MFG or HFG). The offices will be assigned to each group in a balanced way in terms of socio-demographic considerations, depending on their geographical location. It will be done by a Head of Research & Development department in SBT before the study beginning. If, despite randomization, an imbalance occurs within groups due to inter-individual differences such as age, gender, education and disease severity, these factors would be considered as covariant in results analysis.

Each patient will receive a pseudonymized number composed, in order, of the number of the investigating center, the inclusion number for this center and the patient's initials. The SLT will keep the table of correspondence between this number and the first and last name, as well as the address and telephone number for all patients included in his/her center.

4. Procedure

Our study follows a conventional protocol used to evaluate the cognitive and psychological benefits resulting from cognitive training (for a review, [26]) (see Figure 2 and Table 1 for details). Each patient will be seen 21 times (Visit 1 to Visit 21). The content of each visit is described here below. Before the inclusion patients likely to take part in the study will be identified in speech and language therapy practices as part of their regular care. They will be informed by the speech therapist, co-investigator, about the study. The patient will be given any explanation necessary to fully understand the study, as well as an information letter explaining the objectives and the course of the protocol. The speech and language therapist will also give the patient a consent form in duplicate. The patient will be given one week to decide whether to take part in the study.

Inclusion visit - V1

If the patient agrees to take part in the study, the volunteer and the SLT (by delegation) will date and sign two copies of the consent form (one will be kept by the patient, the other will be kept by the SLT).

Assessment visit: pre-training - V2

During this visit, patients will undergo a series of experimental tasks, neuropsychological tests and questionnaires that will serve as a baseline for our primary and secondary outcomes measures of the effectiveness of the training.

Training visits - V3 to V19

Visits 3 to 19 will be devoted to training. These visits will be carried out at a frequency of once a week, preferably on fixed days +/- 1 day. The patient will perform during about 45 minutes a series of short training exercises involving memory, executive functions, processing speed, visuospatial abilities using the Happyneuron Professional software (https://www.happyneuronpro.com). The number and nature of the training sessions will be identical for all participants. However, the difficulty will be adapted automatically by the software according to the patient's performance. The patients and their caregivers are asked not to perform the cognitive exercises outside the training and the SLTs are asked to monitor this throughout the protocol.

For all groups the SLT will appoint, if possible, a fixed day of a week for at office training. If the patient misses this day, it will be rescheduled, if possible, to another day of the same week. For the HFG and MFG groups which must train at home the SLT will fix the day(s) of trainings at home and patients and their caregivers will receive the e-mail in the morning of the training day. If, despite of this, patient will forget to train they will be allowed to train another day of the week. The SLT will be able to check whether or not the patient trained on the scheduled day and if necessary, will contact patient or his/her caregiver to reschedule the training for the next day. Patients are also informed that they can ask the caregiver for a technical problem or to call his/her SLT.

Assessment visit: post-training - V20

During this visit patients will perform the same assessments as in the pre-training. This will allow intra-group and inter-group comparisons of the effectiveness of the training in the three training conditions.

Assessment visit: long-term follow-up - V21

During this visit, patients will complete the same assessments as in the pre-training and post-training visits. This will allow intra- and inter-group comparisons of the sustainability of training effectiveness.

Table 1. The main steps of the protocol process with the timetable.

Steps	V0 Pre-inclusion	V1 Inclusion	V2 Assessment T0	V3 to V19 Training	V20 Assessment T1	V21 Assessment T2
Time / Actions	D-30 à D-15	D0	W1	W2-W17	W18	W30
Allocation	X					
Eligibility screen	X					
Study presentation to the patient	X					
Signature of the informed consent		X				
Assessments (Neuropsychological tests, questionnaires and experimental tasks)			X		X	X
Cognitive training						
Group REG				X		
Group HFG				X		
Group MFG				X		
Collection of adverse events			X	X	X	X

Note: V = Visit; W = Week; D = Day; T = Time of assessment; REG = regular group; HFG = high frequency group; MHG = moderate frequency group.

5. Primary measures of training benefits

In order to test the effects of the training we will use three types of objective measures: experimental tasks, neuropsychological tests, and questionnaires. Our primary outcome measures are the scores obtained by patients with AD in executive and working memory experimental tasks. Our secondary outcome measures are the scores that patients will obtain on neuropsychological tests and questionnaires that will provide information on the overall level of improvement and above all, provide answers on the effect of the training on well-being and self-esteem. We will calculate the composite scores for our primary outcome measures. All measures will be performed in the three time-points (T0 – pre-training, T1 – immediately after training, and T2 – 3 months after training). The choice of these measures was made according to the trained cognitive functions and the cognitive (working memory, executive functions) and psychological (self-esteem, motivation, psychological state - depression/anxiety, assessment of quality of life) domains for which training benefits are expected. These evaluations enable us to first determine the baseline level of patient's cognitive capacities and his or her emotional and motivational state and second to measure the training benefice by comparing

the pre-training results (T0) with those obtained immediately after the end of the training (T1) and 3 months later (T2).

5.1 Neuropsychological tests

Verbal Fluency [27]

The overall objective of the fluency test is to evaluate executive functions by accessing patient's capacity to access their lexical repertoire according to a given letter or a semantic category.

TMT A/B [28]

Trail Making Test consists of two parts. Part A measure processing speed – the patient must connect in ascending order the 25 numbers randomly distributed in circles on the A4 page. Part B measure cognitive flexibility – the patient must perform the same task as in part A while alternating between numbers and letters (i.e., 1-A-2-B-3-C, etc.).

Logical Memory [29]

Logical Memory I and II are subtests of the *MEM Wechsler IV*. Each correctly recalled detail out of 25 details per story is scored 1 point, giving the maximum raw score of 50 points for two stories. Logical Memory II is a delayed condition of Logical Memory I. The test ends with recognition, in which patient must answer a series of questions concerning each story.

MMSE [30]

The Mini Mental State Examination (MMSE) is a commonly used test for screening general cognitive impairment. The maximum MMSE score is 30 points.

Digit Span [29]

Two types of spans are used, forward and backward to measure respectively short-term and working memory. For both span the test ends if the participant fails to repeat two consecutive series. The maximum score is 48.

5.2 Questionnaires

Geriatric Depression Scale (GDS) 30 items [31]

GDS is 30 items**,** self-reported scale that uses "Yes/No" responses. It is used to detect the symptoms of depression in older adults. Scores of 0-4 are considered normal, 5-8 indicate mild depression; 9-11 indicate moderate depression; and 12-15 indicate severe depression.

Questionnaire of Cognitive Complaint [32]

It is a yes/no 10 questions survey targeting memory, language, orientation, and behavior, enabling clinicians to distinguish between a benign cognitive complaint and an at-risk complaint.

Instrumental Activities of Daily Living (IADL) [33]

Eight areas of daily functioning are measured with IADL scale, with a score ranging from 0 (dependent) to 8 (independent) for women and from 0 to 5 for men.

Pittsburgh Sleep Quality Index (PSQI) [34]

It is used to measure quality and sleep cycles in older adults by assessing seven sleep domains. It is self-reported measure giving a global score ranging from 0 (no difficulties) to 21 (severe difficulties), with the score higher than 5 reflecting disturbance of sleep and its quality.

SF 12 [35]

It is a self-reported 12 questions survey assessing the quality of life and more specifically the incidence of health condition on daily living by exploring 8 areas. Two scores are calculated – a mental component score (MCS-12) and a physical component score (PCS-12).

Motivation scale for older adults [36]

This scale measures intrinsic motivation, extrinsic self-determined and non-self-determined motivation and amotivation in different life contexts. There are 12 motivational statements per life context. Each of the statements is evaluated on a scale of 1 to 7 points.

5.3 Experimental Tasks

Four experimental tasks were constructed to measure near transfer of the effects of the training on executive functions and memory, the cognitive functions targeted by the training.

Stop Signal [37]

This task evaluates inhibition capacities. The participant is asked to give a response to the presentation of a target stimulus (Go signal) and to prevent this response when the stimulus is followed or preceded by a beep (Stop signal). The task includes two phases. The mean reaction time for each participant is calculated to be used in a second phase as a reference time for auditory signal presentation. In total, there are 96 trials. The trails are presented in randomized manner. The auditory signal presentation is adaptive. The first signal is presented after the stimulus presentation at reference time calculated in the phase 1. Each following signal is presented depending on the participant's capacity to withhold his/her response. If the participant succeeds, the time is increased by 10ms, if the participant fails the time is decreased by 10ms.

Letter and number pairs [38]

This task is used to evaluate mental flexibility. The participant sees 4 blocks of 48 letter-number pairs giving in total 192 trials presented in aleatory manner. Each pair appears for 350 ms on a computer screen, either in a square located in the upper part of the screen or in a square located in the lower part of the screen. The participant is asked to make a parity judgement if the pair appears at the upper part of the screen, and to make consonant/vowel judgement if it appears at the lower part of the screen. Reaction time and accuracy are recorded.

Up-dating span [38]

This task is used to evaluate up-dating in working memory. The series of letters appear on a computer screen, the participant is asked to memorize the last three presented letters, without knowing the length of the series. The series are presented in random order. Reaction time and accuracy are recorded.

Operation reading letters span [39]

This task is used to evaluate working memory. It consists of 8 series of 2 to 5 letters. The letters are separated by a presentation of one, two or three operands composed of one or two digits. The participant is asked to memorize each series of letters while reading aloud between each letter the operations and their results. In the end of the series the participant is asked to recall in serial order the letters.

6. Computer-based cognitive training

Training will be done for each participant over a period of 4 months on the PC computer with the Happyneuron Pro software (https://www.scientificbraintrainingpro.fr). Patients will realize the training as indicated in Design section, page 5. In the beginning of each session SLT will ask participant to report any event that have occurred during the week and could in any way disturb his/her participation to the training. These events will be reported in the EON. A 4-months training period is justified by the fact that we wish to evaluate the benefits of a fairly short period that would be less prone to drop out and whose duration is sufficient, according to the literature, to produce benefits [40 - 41]. We choose the training tool, Happyneuron Pro[2], because it is a for well-known product cognitive remediation and frequently used by the SLTs in France, and in particular by SLTs participating to our study. Research and clinical studies have shown the effectiveness of the training

[2] Happyneuron Pro is a product developed by Scientific Brain Training.

programs proposed in the Happyneuron Pro software in improving cognitive functioning in patients suffering from different diseases and in normal aging [42 - 47]

Each training session of about 45 minutes includes 10 exercises of different durations, but not exceeding 4 minutes (see Table 2 for details). The training program automatically stops after 45 minutes, even if the patient has not completed the 10 exercises scheduled for the session. However, the session stops after the patient ended the in-hand exercise. The patients are not informed about the number of exercises they will perform during each session, they only know that each session will approximately last for 45 minutes. The training is adaptable from session to session. Thus, each session begins on the exercise and the level on which the previous session stopped. Each exercise has 9 levels of difficulty, and each level is displayed at least twice. This is because the criterion for passing to a higher level of difficulty is to successfully execute the current level two consecutive times.

The training targets the following cognitive functions: working and short-term memory, executive functions, visuo-spatial capacities, and processing speed (see Table 2 for more details).

Table 2. Exercises included in cognitive training and cognitive capacity targeted by the exercise.

Game type	Cognitive capacity targeted by the exercise
1- Tower of Hanoi	- Problem solving
2- Put some order in these accounts	- Visuospatial exploration - Attention and numerical processing
3- Bird songs	- Auditory memory - Memorizing strategies
4- Objects, where are you?	- Visuospatial memory - Binding capacities
5- Find your way back.	- Visual short-term memory - Working memory
6- Blazon Game	- Visual memory - Attention - Visuospatial perception
7- Waiter please	- Verbal memory - Visual memory - Mental rotation ability
8- Conduct the investigation	- Lexical comprehension - Categorization skills
9- It is up to you to count	- Working memory - Mental arithmetic
10- You have got a message	- Verbal-auditory memory

7. Equipment and programming

The SLT's office and patient's personal computers are the only equipment used to run our protocol. All questionnaires and neuropsychological tests (except TMT and Figure from MMSE) were digitalized on

Typeform. Experimental tasks were designed and programmed on the Open Sesame free access Software (Version 3.2.5). Thus, this software was installed on the SLT's computers. The training sessions were programmed on Happyneuron Pro Platform https://www.scientificbraintrainingpro.fr/

8. Study Management

8.1 General management

Each SLT participating in the study was provided an appropriate training to use all tools necessary for conducting the protocol. The training was delivered during videoconferences in small groups or individually and completed by e-mail exchanges and video tutorials, digital user guide, and power point presentations.

Each SLT has two personal spaces secured by password, one on the Happyneuron Pro platform to manage the trainings and another one on the Ennov Clinical containing the electronic observation notebooks (EON) of the patients to store all clinical information and results of neuropsychological tests and experimental tasks for each patient. It is hosted on the secured platform of Hospices Civils de Lyon (HCL). These personal areas are supervised by principal investigator, junior investigator of this study, and a clinical research assistant of HCL.

The workspace on Happyneuron Pro platform is used to create the training area for each included patient and to specify the frequency per week and the days of training sessions, depending on the training group. Once the patient's space is created and the sessions scheduled, the patient receives a link by email on the scheduled days and all he must do to access the training, is to click on the link.

The monitoring of the study is done by the Department of Clinical Research and Innovation of the Hospices Civils of Lyon[3]. A designed clinical research assistant is in charge of the monitoring that includes:

- a study start-up visit to the coordinating center and the inclusion centers,
- a mid-term visit
- a closing visit

During mid-term and closing visits the verification of consent forms and EON will be done.

[3] HCL's identification code for the study 69HCL18_0881

The coordinating center is composed of the three investigators (principal, senior and junior investigator) who designed the protocol and will be in charge of verification of inclusion/exclusion criteria before patient's inclusion to the study and in the analysis of the data. These investigators are not involved in data collection.

8.2. Data management and storage

The performance on the neuropsychological tests conducted via Typeform are automatically recorded. When they are completed an email with the patients' scores is automatically sent to the investigator and the SLT, and patients scores can be extracted from Typeform on Excel. In the end the SLT enters the scores of interests into the patient's EON.

Performances on the experimental tasks are recorded on the SLT's office computer and then the scores of interests are entered into the patient's EON.

The training results for each session are automatically recorded on a secure server hosted by a health data host. There is no transit between servers, no storage of data on the patient computer. SLTs have the possibility to monitor the trainings remotely: this is possible by accessing the patient's space, enabling the SLTs to check if the training has been regularly carried out and to follow patients' progression. If necessary, the SLT can also access the results online.

All the data entered in EON are accessible during the period of inclusion and after the end of the study to the clinical research assistant in charge of the study monitoring and to the three investigators in charge of this study and who do not take part in the data collection. The data extraction and analysis are allowed at two points of the study, mid-term, and the end of inclusion period. The final trial dataset that will be used for statistical analysis will be accessible to the three investigators in charge of this study.

9. Statistical considerations

9.1 Estimation of samples size

The sample size per training group was estimated on previous protocols and literature reviews [8, 48] which show that the number of patients included in protocols varies between 15 and 150 per group. taking into account the data of previous studies and expected size effect, we decided to include 55 patients per group. Indeed, the size of each group was estimated to be 45, assuming a small effect of the intervention (Cohen's d = 0.40), with a repeated measures factor Time of assessment (pre-training, immediate post-training, long term post-training) and an independent measures factor of Group (MFG, HFG, REG) to reach a power of 0.8 with an alpha at 0.05. We have estimated a 10% dropout rate by

the participants. Thus, we have estimated the inclusion of 50 patients per group. In addition, to consider the cluster randomization we have estimated that we should increase our sample by 10%, bringing the number of patients per group to 55. This number is compatible with our capacity of patients' recruitment.

9.2 Statistical methods description

Linear models are considered for all behavioral measures collected with one random intercept per patient and one per practice. The analysis will concern independent measures factor Group with three modalities (MFG, HFG, REG) and repeated measures factor Time with three modalities (T0 - pre-training, T1 - post-training, T2 - long term monitoring) and the interaction between these two factors. Level of significance is fixed to 0.05. In our longitudinal analysis, we risk floor, ceiling, and curvilinear effects since we have stopped the inclusion at an MMSE score higher than 15. For that reason, we plan to adjust the initial values first, and to avoid the biases linked to the adjustment, we will refer to the DAG (Causal Directed Acyclic) Graph. We will then apply methods that take into account the floor and curvilinear effects, by adjusting the mean value of the observations, then through a linear mixed model in a structural model we will study the evolution on the time axis and the common effects of the co-variables.

The interim analyses are also planned, using the same models as described above, at three time points: 1 - after inclusion of 15 patients in each group, 2 - after inclusion of 30 patients in each group, and 3 - after inclusion of 40 patients in each group. We decided to perform interim analyses to see if trends would emerge on smaller samples than those estimated by the power analysis to be necessary to obtain a training effect. These analyses are not intended to modify the protocol or the planned inclusions.

Statistical analyses will be carried out using STATISTICA software.

10. Risks and benefits

There is no particular risk for patients to participate in this study. The only drawbacks could be computer-related fatigue, especially for patients included in HFG.

The major personal benefit for patients would be an improvement in their cognitive and emotional state or a slowing of the cognitive deficit progression. The secondary benefit could be the improvement of their quality of life.

There is also a collective benefit since if the results of this study confirm our hypothesis, we could give recommendations concerning at home training.

11. Ethics and dissemination

The study is conducted with ethics approval of the national ethical committee (CPP – Comité de Protection des Personnes, Sud Méditerranée III, Nr. 2019) and of the National Commission for Information Technology and Liberties (Nr. 919217). Any modification to the study design has to be communicated to the clinical research assistant and if necessary, a request for amendment must be addressed to the national ethical committee who has delivered the approval for the study. The results of the study will be disseminated in the form of oral communications or posters in international scientific conferences and seminars for healthcare professionals (e.g., Alzheimer's Association International Conference, Union Nationale pour le Dévelopment de la Recherche et de l'Evaluation en Orthophonie) and published in a scientific journal in the field (e.g., Journal of Alzheimer's Disease). The communications are allowed after the first statistical analyses planed at the mid-time period of inclusion.

12. Significance

In a general way this study will contribute to the knowledge of cognitive training effects on cognition in patients with AD in the prodromal to moderate stages. The comparison of results obtained for neuropsychological tests, questionnaires, and experimental tasks by REG patients with those obtained by MFG patients will inform about the effects of at home cognitive training done as a complement to training performed in SLT office. This will provide clear indications as about the usefulness of this type of cognitive training program for patients with AD. Comparison of results obtained by MFG patients with those obtained by HFG patients will provide indications regarding the best necessary frequency of the training sessions.

Beyond the benefits of cognitive training on the cognition of patients with AD, and the importance of trying to determine the best frequency to obtain the optimal effects, other issues, that are independent of the cognitive training program, may impact its success if they are not carefully considered. AD has an important impact on autonomy, emotional balance, and motivation, very often linked to self-esteem [18-20]. Thus, it seems important, when designing cognitive training protocols for patients with AD to consider psychological, environmental and autonomy factors for a more optimal cognitive training plan, that seeks the well-being of the individual as a whole [20,48-49]. Through questionnaires administered in our protocol [31-36], we hope to shed light on the emotional benefits of training and answer questions regarding the commitment and adherence to the program

patients with AD as well as to provide a more informed opinion on the importance of seeking assistance from a third party. Understanding whether the same issues of autonomy in training are involved for patients with mild and moderate AD will allow us to elaborate more precise computer-based home training protocols for different patient's profile. These protocols should take into consideration the cognitive decline severity that may affect autonomy in training as cognitive impairment increases. Such considerations will bring us to foresee solutions when it comes to training performed at home for those who are less autonomous.

Authors Contribution

Author Contributions: Conceptualization, S.D. and H.C.; Data treatment, S.D.; Project administration, S.D. and H.C., Supervision, H.C., F.T-B., B.C.; Writing—Original draft, S.D. and H.C.; Writing—Review & editing, S.D., H.C., F.T-B. and B.C. All authors have read and agreed to the submitted version of the manuscript.

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Competing interests' statement

Franck Tarpin-Bernard and Bernard Croisile are cofounders and shareholders of SBT Humans Matter.

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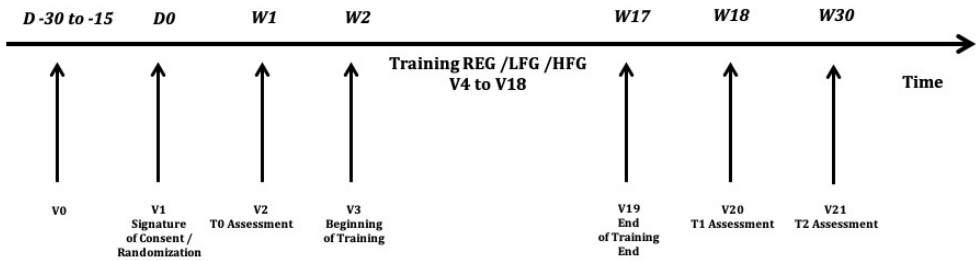
Figure legend

Figure 1: illustrating on the time axis the evolution of the experiment with the facts marked on a weekly basis trainings take place between the 2nd and the 17th week for the 3 training groups simultaneously. Note: V = Visit; W = Week; D = Day; T = Time of assessment; REG = regular group; HFG = high frequency group; MHG = moderate frequency group.



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321x118mm (72 x 72 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	7
Protocol version	#3	Date and version identifier	5
Funding	#4	Sources and types of financial, material, and other support	19
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1;19

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	n/a
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	6

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-9
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n/a

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5-6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7-9; 11
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	13
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	13
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	13
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13-14
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	19
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Study design and protocol of a low to high intensity computer-based cognitive training at home in supplement to standard care in patients with AD

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Primary Subject Heading:	Rehabilitation medicine
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Keywords:	GERIATRIC MEDICINE, Dementia < NEUROLOGY, MENTAL HEALTH, PREVENTIVE MEDICINE, Delirium & cognitive disorders < PSYCHIATRY, COMPLEMENTARY MEDICINE

Study design and protocol of a low to high intensity computer-based cognitive training at home in supplement to standard care in patients with AD

Samar Dimachki[1,3], Franck Tarpin-Bernard[3], Bernard Croisile[2,3] & Hanna Chainay[1]

[1] Laboratoire d'Étude des Mécanismes Cognitifs, Université Lyon 2, Bron, France

[2] Service de Neuropsychologie, Centre Mémoire de Ressource et de Recherche de Lyon, Hôpital Neurologique, Bron, France

[3] Scientific Brain Training SA, Lyon, France

samar.dimachki@univ-lyon2.fr

f.tarpin@humansmatter.co

bernard.croisile@wanadoo.fr

hanna.chainay@univ-lyon2.fr

Corresponding author: Samar Dimachki

Université Lyon 2

Laboratoire d'Étude des Mécanismes Cognitifs

5 avenue Pierre Mendès France

69676 Bron, France

E-mail : samar.dimachki@univ-lyon2.fr

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Abstract

Introduction: Recent studies on cognitive training in patients with Alzheimer's disease (AD) showed positive long-term effects on cognition and daily living, suggesting remote computer-based programmes to increase training sessions while reducing patient's travelling. The aim of this study is to examine short- and long-term benefits of computer-based cognitive training at home in patients with mild to moderate AD, as a complement to the training in speech and language therapists' (SLT) offices. The secondary purpose is to study training frequency required to obtain noticeable effects.

Methods and analyses: This is a national multi-centre study, conducted in SLT offices. The patients follow training in one of three conditions: once a week in SLT office only (regular condition) and once a week in SLT office plus one or three times per week at home. The trainings' content in SLT office and at home is identical. For all three groups near and far transfer will be compared to evaluate training frequency's effect. Our primary outcome is executive and working memory scores in experimental tasks, and the secondary is neuropsychological tests and questionnaires' scores. Linear models' analyses are considered for all measures with a random intercept for patients and another for per practice. The fixed effects will be: three modality Groups and Time, repeated measures, (T0- pre-training, T1 - post-training, T2 - long-term follow-up) and the interaction pairs.

Ethics and dissemination: The study got ethics approval of the national ethical committee CPP Sud Méditerranée III (Nr. 2019-A00458-49) and of the National Commission for Information Technology and Liberties (Nr. 919217). Informed consent is obtained from each participant. Results will be disseminated in oral communications or posters in international conferences and published in scientific journals.

Trial registration number: ClinicalTrials.gov identifier (NCT04010175).

Keywords: Alzheimer's disease, MCI, computer-based cognitive training, at home cognitive training, cognitive benefits, quality of life

Strengths and limitations of the study

► This study will provide information on the short- and long-term effects of remote computer-based cognitive training in addition to regular training in SLT office for patients with AD.

► This study will shed light on the optimal cognitive training frequency to be administered.

► This study will evaluate the adherence to the computer-based programme at home compared to training conducted exclusively in the SLT's office, as this factor is likely to be favourable to the adherence given the reduction in travel and training in a familiar environment.

► The limitation of the present study is that it will not control for the familiarity of the patients with AD with the computer tool, nor for their degree of autonomy in completing remote training by themselves.

INTRODUCTION

Considering increasing occurrence of neurodegenerative disorders in the older adults, such as Alzheimer's disease (AD), and in the absence of effective drug treatment, cognitive training appears to be a promising alternative in healthy and pathological aging for improving cognitive functioning [1-3] and quality of life [4-5]. For some researchers cognitive training is also an added value to drug treatment, as it has been observed to enhance the expression of drug effects [6].

The efficacy of cognitive training in patients with AD is still under the debate [8], especially regarding the best methodological approaches to optimize the training outcomes [9-10], including training feasibility, patient commitment, and motivation. The computer-based cognitive training (CBCT) seems to have several advantages as it provides wide variety of well-calibrated exercises and allows, for example, to easily adapt their difficulty to each patient [11]. The short- and long-term benefits of CBCT were first shown in healthy older adults [7,12,13], but have also been proven in patients with AD and MCI [14-18].

Several studies have highlighted the importance of some criteria that are essential for successful training, whatever its type [19, 15, 20]. Overall, studies recommend early intervention with sessions between 30 minutes and 1 hour and session's frequency of several times a week [9-10, 21]. Such a design is supposed to maintain strong commitment and motivation throughout the training, which is essential for its effectiveness. However, these recommendations face some important problems that make their application difficult. First, few people are concerned about small changes in performance, the majority will only consult when symptoms become more pronounced, which prevents the early intervention suggested by several authors [21-25]. Second, involving patients in high-frequency cognitive training protocols faces several difficulties, the most important of which is frequent travel between home and speech and language therapist's office (SLT). As the disease progresses, autonomy is compromised, and the need of a caregiver's assistance is an additional difficulty. In addition, the change of seasons brings many health problems that interfere with training and often lead to interruptions. One way of circumventing these problems would be to offer a CBCT including some sessions at home [26,17]. Our main hypothesis is that remote cognitive training using computer-based programmes is an effective way to increase the cognitive and psychological benefits of training as an outcome of training. We also hypothesized that more frequent training (e.g., several times per week) should bring greater benefits than training performed once a week.

The primary objective of the present study is to examine the short- and long-term benefits of at home CBCT as a complement to in-office CBCT in patients with mild to moderate AD. The secondary

objective is to evaluate the best frequency of the at home training. To do this, we administer computer-based cognitive training for 4 months under three conditions: (1) in SLT's office once a week, (2) in SLT's office once a week plus once at home, and (3) in SLT's office once a week plus three times at home.

Method

1. Design

This is an experimental study with minimal risks, with 3 parallel groups, namely the training group at the SLT's office only (REG – regular group), the group at the SLT's office plus one session per week at home (MFG - moderate frequency group) and the group at the SLT's office plus three session per week at home (HFG – high frequency group). Patients will be included for 2 years, starting on 1st September 2020 and ending 1st September 2022. For each participant, the inclusion period is approximately 8 months. During this period, participants cannot be included in other protocols that may influence their cognitive or emotional functions. Patients and their caregivers are informed of this point before signing the informed consent and the SLTs are asked to monitor them throughout the protocol. The total duration of the study is 32 months. All inclusions and testing will be carried out in SLT offices. The training will be done in SLT offices and at patients' homes (see Figure 1 for a study design). The content of the training in SLT office and at home is identical.

This study obtained the authorization of the national ethical committee CPP Sud Méditerranée III (Nr. 2019-A00458-49, version 5 from 18/11/2019) and of the National Commission for Information Technology and Liberties (Nr. 919217) and was registered on clinicaltrials.gov (NCT04010175).

1.1 Patient and Public Involvement:

patient and public were not involved.

Figure 1: illustrating on the time axis the evolution of the experiment with the facts marked on a weekly basis trainings take place between the 2nd and the 17th week for the 3 training groups simultaneously. Note: V = Visit; W = Week; D = Day; T = Time of assessment; REG = regular group; HFG = high frequency group; MHG = moderate frequency group.

2. Participants

This study concerns people 60 years or older with a diagnosis of prodromal to moderate Alzheimer's disease. To recruit participants, we contacted SLTs subscribers to SBT's Happyneuron Pro digital tools through the SBT Humans Matter company network. They first answered a questionnaire to identify SLTs practicing with patients with AD. These SLT received a letter of invitation to participate in our study. Eventually, 27 SLTs from different regions of France joined the study and become clinical investigation centres (CIS). A complete list of these SLTs can be obtained from the Department of Clinical Research and Innovation of the Hospices Civils of Lyon[1]. Each SLT is responsible for presenting the study in his or her office to patients whose profile matches our inclusion criteria (for details on eligibility criteria see Box 1). Interested patients will receive the information and consent leaflets. At the next visit, they are asked if they wish to participate to the study, and if so, they sign the informed consent. Thus, the patients are included by the SLTs who also sign an informed consent after validation by the neurologist, the Principal Investigator of this study. Patients are informed that during the study they cannot take part in any other study that could potentially have an effect on their cognitive functions.

2.1 Eligibility

The eligibility criteria are presented in Box 1.

Box 1. Eligibility criteria

Inclusion criteria:

1. Age ≥ 60 years
2. Native French speaker
3. Diagnosis of Alzheimer's disease according to the DSM V criteria
4. Mild to moderate cognitive impairment as stage of disease progression (Mini-Mental State Examination score superior to 15)
5. Unchanged psychotropic treatment in the month prior to inclusion
6. Signed informed consent for a participation to the study (personally or by a legal representative)

Exclusion criteria:

1. Uncorrected vision or hearing impairments
2. Motor dysfunction symptoms that could prevent the tests from being carried out
3. Not having a computer preventing cognitive training at home
4. Receiving SLT care for more than 3 months
5. Refusal to participate in the study
6. Being under guardianship or curatorship

[1] Direction de la Recherche Clinique, Hospice Civil de Lyon
3, quai des Célestins, 69229 Lyon Cedex 2

2.2 Withdrawal Criteria

Each patient is free to withdraw from the study at any time without giving reasons, simply by informing one of the investigators. In case of withdrawn of consent, the data collected up to the date of withdrawal will be analysed.

3. Randomization and Pseudonymization Method

To avoid any unequal treatment of patients in the same SLT, we decided to randomize SLTs' offices into different training groups, instead of randomizing the patients. Thus, each office will be assigned to one of the training groups and all patients included in that SLT office will follow the same training procedure (REG, MFG or HFG). Offices will be allocated to each group in a balanced way in terms of socio-demographic considerations, depending on their geographical location. This allocation will be done by a manager from the SBT Research & Development department before the study beginning. If, despite randomization, an imbalance occurs within groups due to inter-individual differences such as age, gender, education and disease severity, these factors will be considered as covariates in the analysis of results.

Each patient will receive a pseudonymized number consisting of, in order, of the number of the investigating centre, the inclusion number for this centre and the patient's initials. The SLT will keep the table of correspondence between this number and the first and last name, as well as the address and telephone number for all patients included in his/her centre.

4. Procedure

Our study follows a conventional protocol used to evaluate the cognitive and psychological benefits of cognitive training (for a review, [27]) (see Figure 1 and Table 1 for details). Each patient will be seen 21 times (Visit 1 to Visit 21). The content of each visit is described here below. Prior to inclusion, patients likely to take part in the study will be identified in the SLT offices as part of their regular care. They will be informed by the speech and language therapist, co-investigator, about the study. The patient will be given any explanation necessary for a good understanding of the study, as well as an information letter explaining the objectives and the course of the protocol. The speech and language therapist will also give the patient a consent form in duplicate. The patient will have one week to decide whether to take part in the study.

Inclusion visit - V1

If the patient agrees to take part in the study, the volunteer and the SLT (by delegation) will date and sign two copies of the consent form (one will be kept by the patient, the other will be kept by the SLT).

Assessment visit: pre-training - V2

During this visit, patients will undergo a series of experimental tasks, neuropsychological tests and questionnaires that will serve as a baseline for our primary and secondary outcomes measures of training effectiveness.

Training visits - V3 to V19

Visits 3 to 19 will be devoted to training. These visits will be carried out at a frequency of once a week, preferably on fixed days +/- 1 day. The patient will perform a series of short training exercises involving memory, executive functions, processing speed, visuospatial abilities for approximately 45 minutes using the Happyneuron Professional software (https://www.happyneuronpro.com). The number and nature of the training sessions will be identical for all participants. However, the difficulty will be adapted automatically by the software according to the patient's performance. Patients and their caregivers will be asked not to perform the cognitive exercises outside of training and the SLTs will be asked to monitor this throughout the protocol.

For all groups the SLT will, if possible, designate a fixed day of the week for in-office training. If the patient misses this day, it will be rescheduled, if possible, to another day of the same week. For the HFG and MFG groups which are to train at home, the SLT will schedule the day(s) for trainings at home and patients and their caregivers will receive the e-mail on the morning of the training day. If, despite of this, patient forgets to train they will be allowed to train another day of the week. The SLT will be able to check whether or not the patient has trained on the scheduled day and, if necessary, will contact patient or his/her caregiver to reschedule the training for the next day. Patients will be also informed that they can ask the caregiver to solve for a technical problem or to call his/her SLT.

Assessment visit: post-training - V20

During this visit, the patients will complete the same assessments as during the pre-training. This will allow comparison of the effectiveness of the training in the three training conditions within and between groups.

Assessment visit: long-term follow-up - V21

During this visit, the patients will complete the same assessments as in the pre-training and post-training visits. This will allow for intra- and inter-group comparisons of the sustainability of the training effectiveness.

Table 1. The main steps of the protocol process with the timetable.

Steps	V0 Pre-inclusion	V1 Inclusion	V2 Assessment T0	V3 to V19 Training	V20 Assessment T1	V21 Assessment T2
Time / Actions	D-30 à D-15	D0	W1	W2-W17	W18	W30
Allocation	X					
Eligibility screen	X					
Study presentation to the patient	X					
Signature of the informed consent		X				
Assessments (Neuropsychological tests, questionnaires and experimental tasks)			X		X	X
Cognitive training						
Group REG				X		
Group HFG				X		
Group MFG				X		
Collection of adverse events			X	X	X	X

Note: V = Visit; W = Week; D = Day; T = Time of assessment; REG = regular group; HFG = high frequency group; MHG = moderate frequency group.

5. Primary measures of training benefits

In order to test the effects of the training, we will use three types of objective measures: experimental tasks, neuropsychological tests, and questionnaires. Our primary outcome measures are the scores that patients with AD will obtain in executive and working memory experimental tasks. Our secondary outcome measures are the scores that patients will obtain on neuropsychological tests and questionnaires that will provide information on the overall level of improvement and, more importantly, answers on the effect of training on well-being and self-esteem. We will calculate the composite scores for our primary outcome measures. All measures will be taken at the three time-points (T0 – pre-training, T1 – immediately after training, and T2 – 3 months after training). The choice of these measures was made according to the cognitive functions trained and the cognitive (working memory, executive functions) and psychological (self-esteem, motivation, psychological state - depression/anxiety, assessment of quality of life) domains for which training benefits are expected. These assessments allow us to, first, determine the baseline level of the patient's cognitive abilities and their emotional and motivational state and, second, to measure the benefit of training by

comparing the pre-training results (T0) with those obtained immediately after the end of the training (T1) and 3 months later (T2).

5.1 Neuropsychological tests

Verbal Fluency [28]

The general aim of the fluency test is to assess executive functions by evaluating patient's ability to access their lexical repertoire in relation to a given letter or a semantic category.

TMT A/B [29]

Trail Making Test consists of two parts. Part A measures processing speed – the patient must connect in ascending order the 25 numbers randomly distributed in circles on page A4. Part B measures cognitive flexibility – the patient has to perform the same task as in part A while alternating numbers and letters (i.e., 1-A-2-B-3-C, etc.).

Logical Memory [30]

Logical Memory I and II are subtests of the *Wechsler MEM IV*. Each correctly recalled detail out of 25 details per story is scored 1 point, giving the maximum raw score of 50 points for two stories. Logical Memory II is a delayed condition of Logical Memory I. The test ends with recognition, in which patient must answer a series of questions about each story.

MMSE [31]

The Mini Mental State Examination (MMSE) is a commonly used test for screening general cognitive impairment. The maximum score of the MMSE is 30 points.

Digit Span [30]

Two types of spans are used, forward and backward, to measure short-term and working memory respectively. In both cases, the test ends if the participant fails to repeat two consecutive series. The maximum score is 48 points.

5.2 Questionnaires

Geriatric Depression Scale (GDS) 30 items [32]

The GDS is 30 item self-reported scale that uses "Yes/No" responses. It is used to detect the symptoms of depression in older adults. Scores of 0 to 4 are considered normal, 5 to 8 indicate mild depression, 9 to 11 moderate depression and 12 to 15 severe depression.

Questionnaire of Cognitive Complaint [33]

This is a 10-question yes/no questionnaire covering memory, language, orientation and behavior, allowing clinicians to distinguish a mild cognitive complaint from an at-risk one.

Instrumental Activities of Daily Living (IADL) [34]

Eight domains of daily functioning are measured with the IADL scale, with scores ranging from 0 (dependent) to 8 (independent) for women and from 0 to 5 for men.

Pittsburgh Sleep Quality Index (PSQI) [35]

It is used to measure quality and sleep cycles in older adults by assessing seven sleep domains. It is a self-reported measure giving a global score ranging from 0 (no difficulties) to 21 (severe difficulties), with scores above 5 reflecting disturbances of sleep and sleep quality.

SF 12 [36]

This is a 12-question self-reported survey assessing the quality of life and more specifically the impact of health condition on daily life by exploring 8 domains. Two scores are calculated – a mental component score (MCS-12) and a physical component score (PCS-12).

Motivation scale for older adults [37]

This scale measures intrinsic motivation, self-determined and non-self-determined extrinsic motivation and amotivation in different life contexts. There are 12 motivational statements per life context. Each of these statements is rated on a scale of 1 to 7 points.

5.3 Experimental Tasks

Four experimental tasks were constructed to measure the near transfer of training effects on executive functions and memory, the cognitive functions targeted by the training.

Stop Signal [38]

This task evaluates inhibition skills. The participant is asked to give a response to the presentation of a target stimulus (Go signal) and to prevent this response when the stimulus is followed or preceded by a sound signal (Stop signal). The task consists of two phases. The mean reaction time for each participant is calculated to be used in a second phase as a reference time for the presentation of the auditory signal. In total, there are 96 trials. The trials are presented randomly. The presentation of the auditory signal is adaptive. The first signal is presented after the stimulus at reference time calculated in the phase 1. Each subsequent signal is presented according to the participant's ability to withhold the response. If the participant succeeds, the time is increased by 10ms, if the participant fails, the time is decreased by 10ms.

Letter and number pairs [39]

This task is used to assess mental flexibility. The participant sees 4 blocks of 48 letter-number pairs, i.e. a total of 192 randomly presented trials. Each pair appears for 350 ms on a computer screen, either in a square located in the upper part of the screen or in a square located in the lower part of the screen. The participant is asked to judge the parity if the pair appears at the upper part of the screen, and to make consonant/vowel judgement if it appears at the lower part of the screen. Reaction time and accuracy are recorded.

Up-dating span [39]

This task is used to assess the updating in working memory. Series of letters appear on a computer screen, the participant is asked to memorize the last three letters presented, without knowing the length of the series. The series are presented in random order. Reaction time and accuracy are recorded.

Operation reading letters span [40]

This task is used to assess working memory. It consists of 8 series of 2 to 5 letters. The letters are separated by a presentation of one, two or three operands consisting of one or two numbers. The participant is asked to memorize each series of letters while reading aloud between each letter the operations and their results. At the end of the series, the participant is asked to recall the letters in the order of their presentation.

6. Computer-based cognitive training

The training will be done for each participant over a period of 4 months on the PC using the Happyneuron Pro software (https://www.scientificbraintrainingpro.fr). Patients will complete the training as described in Design section, page 5. At the beginning of each session, the SLT will ask the participant to report any event that have occurred during the week that may, in any way, disturb his/her participation in the training. These events will be reported in the EON. The rational for a 4-month training period is that we wish to evaluate the benefits of a relatively short period of time that would be less prone to drop-out and that is of sufficient duration, according to the literature, to produce benefits [41 - 42]. We choose the training tool, Happyneuron Pro[2], because it is a well-known cognitive remediation product frequently used by the SLTs in France, and in particular by the SLTs participating in our study. Research and clinical studies have shown the effectiveness of the training

[2] Happyneuron Pro is a product developed by Scientific Brain Training.

programmes proposed in Happyneuron Pro software to improve cognitive functioning in patients suffering from different diseases and in normal aging [43 - 48]

Each training session lasts approximately 45 minutes and consists of 10 exercises of varying lengths, but not exceeding 4 minutes (see Table 2 for details). The training programme stops automatically after 45 minutes, even if the patient has not completed the 10 exercises planned for the session. However, the session stops after the patient has completed the exercise in hand. Patients are not informed how many exercises they will perform in each session, only that each session will last approximately 45 minutes. The training is adaptable from session to session. Thus, each session starts with the exercise and the level that the previous session ended with. Each exercise has 9 levels of difficulty, and each level is displayed at least twice. The criterion for moving up to a higher level of difficulty is to successfully perform the current level twice in a row.

The training targets the following cognitive functions: working and short-term memory, executive functions, visuo-spatial abilities, and processing speed (see Table 2 for more details).

Table 2. Exercises included in cognitive training and cognitive capacity targeted by the exercise.

Game type	Cognitive capacity targeted by the exercise
1- Tower of Hanoi	- Problem solving
2- Put some order in these accounts	- Visuospatial exploration - Attention and numerical processing
3- Bird songs	- Auditory memory - Memorizing strategies
4- Objects, where are you?	- Visuospatial memory - Binding capacities
5- Find your way back.	- Visual short-term memory - Working memory
6- Blazon Game	- Visual memory - Attention - Visuospatial perception
7- Waiter please	- Verbal memory - Visual memory - Mental rotation ability
8- Conduct the investigation	- Lexical comprehension - Categorization skills
9- It is up to you to count	- Working memory - Mental arithmetic
10- You have got a message	- Verbal-auditory memory

7. Equipment and programming

The SLT's office and patient's personal computers are the only equipment used to run our protocol. All questionnaires and neuropsychological tests (except TMT and Figure from MMSE) were digitalized on

Typeform. The experimental tasks were designed and programmed on the Open Sesame free access software (Version 3.2.5). This software was therefore installed on the SLT's computers. The training sessions were programmed on Happyneuron Pro Platform https://www.scientificbraintrainingpro.fr/

8. Study Management

8.1 General management

Each SLT participating in the study received an appropriate training in the use of all tools needed to carry out the protocol. The training was provided in small groups or individually videoconferences and complemented by e-mail exchanges and video tutorials, a digital user guide, and power point presentations.

Each SLT has two personal password-protected areas, one on the Happyneuron Pro platform to manage the training and another one on the Ennov Clinical containing the patients' electronic observation notebooks (EON) to store all clinical information and results of neuropsychological tests and experimental tasks for each patient. It is hosted on the secure platform of the *Hospices Civils de Lyon* (HCL). These personal areas are supervised by principal investigator, junior investigator of this study, and a clinical research assistant from the HCL.

The workspace on Happyneuron Pro platform is used to create the training area for each included patient and to specify the weekly frequency and the days of training sessions, depending on the training group. Once the patient's space is created and the sessions scheduled, the patient receives a link by email on the scheduled days and all he /she has to do to access the training, is to click on the link.

The study is monitored by the Clinical Research and Innovation Department of the Hospices Civils of Lyon[3]. A designed clinical research assistant is in charge of the monitoring which includes:

- a study start-up visit to the coordinating centre and the inclusion centres,
- a mid-term visit
- a closing visit

At the mid-term and closing visits, the consent forms and EON will be checked.

[3] HCL's identification code for the study 69HCL18_0881

The coordinating centre is composed of the three investigators (principal, senior and junior investigator) who designed the protocol and will be in charge of verification of the inclusion/exclusion criteria prior to the inclusion of patients in the study and of the data analyses. These investigators are not involved in data collection.

8.2. Data management and storage

The performance on the neuropsychological tests performed via Typeform is automatically recorded. When completed, an email containing the patients' scores is automatically sent to the investigator and the SLT, and patients' scores can be extracted from Typeform into Excel. Finally, the SLT enters the scores of interest into the patient's EON.

Performances on the experimental tasks are recorded on the SLT's office computer and the scores of interests are entered into the patient's EON.

The training results for each session are automatically stored on a secure server hosted by a health data host. There is no transit between the servers, nor is there any storage of data on the patient's computer. SLTs have the option of monitoring the trainings remotely: this is possible by accessing the patient's space, which allows the SLTs to check whether the training has been carried out regularly and to monitor patients' progress. If necessary, the SLTs can also access the results online.

All the data entered in EON are accessible during the inclusion period and after the end of the study to the clinical research assistant in charge of the follow-up of the study and to the three investigators in charge of the study and who are not involved in the data collection. Data extraction and analyses are allowed at two points of the study, mid-term, and the end of inclusion period. The final trial dataset that will be used for statistical analyses will be available to the three investigators in charge of this study.

9. Statistical considerations

9.1 Estimation of samples size

The sample size per training group was estimated on the basis of previous protocols and literature reviews [9, 49] which show that the number of patients included in the protocols varies between 15 and 150 per group. Taking into account the data of previous studies and expected size effect, we decided to include 55 patients per group. Indeed, the size of each group was estimated to be 45, assuming a small effect of the intervention (Cohen's d = 0.40), with a repeated measures factor Time of assessment (pre-training, immediate post-training, long term post-training) and an independent measures factor of Group (MFG, HFG, REG) to reach a power of 0.8 with an alpha at 0.05. We estimated

a 10% dropout of participants. Thus, we estimated the inclusion of 50 patients per group. In addition, to consider the cluster randomization, we estimated that we need to increase our sample by 10%, bringing the number of patients per group to 55. This number is compatible with our capacity to recruit patients.

9.2 Statistical methods description

Linear models are considered for all behavioural measures collected with one random intercept per patient and one per practice. The analysis will concern independent measures factor Group with three modalities (MFG, HFG, REG) and repeated measures factor Time with three modalities (T0 - pre-training, T1 - post-training, T2 - long term monitoring) and the interaction between these two factors. The significance level is set at 0.05. In our longitudinal analysis, we risk floor, ceiling, and curvilinear effects since we have stopped the inclusion at an MMSE score higher than 15. For this reason, we plan to adjust the initial values first, and to avoid the biases linked to the adjustment, we will refer to the DAG (Causal Directed Acyclic) Graph. We will then apply methods that take into account the floor and curvilinear effects, by adjusting the mean value of the observations, and then through a linear mixed model in a structural model we will study the evolution on the time axis and the common effects of the co-variables.

The interim analyses are also planned, using the same models as described above, at three time points: 1 - after inclusion of 15 patients in each group, 2 - after inclusion of 30 patients in each group, and 3 - after inclusion of 40 patients in each group. We decide to perform interim analyses to see if trends would emerge on smaller samples than those estimated by the power analysis to be necessary to obtain a training effect. These analyses are not intended to alter the protocol or planned inclusions.

Statistical analyses will be carried out using STATISTICA software.

10. Risks and benefits

There are no particular risks for patients to participate in this study. The only disadvantages could be computer-related fatigue, especially for patients included in the HFG.

The major personal benefit for patients would be an improvement in their cognitive and emotional state or a slowing of the progression of cognitive impairment. The secondary benefit could be the improvement of their quality of life.

There is also a collective benefit since if the results of this study confirm our hypothesis, we could give recommendations concerning at home training.

11. Ethics and dissemination

The study is conducted with the approval of the national ethics committee (CPP – *Comité de Protection des Personnes, Sud Méditerranée III*, Nr. 2019) and of the National Commission for Information Technology and Liberties (Nr. 919217). Any modification to the study design must be addressed to the clinical research assistant and if necessary, a request for modification must be addressed to the national ethical committee that issued the authorization for the study. The results of the study will be disseminated in the form of oral or posters presentations at international scientific conferences and seminars for health professionals (e.g., Alzheimer's Association International Conference, *Union Nationale pour le Dévelopment de la Recherche et de l'Evaluation en Orthophonie*) and published in a relevant scientific journal (e.g., Journal of Alzheimer's Disease). The presentations are allowed after the first statistical analyses planned at the mid-point of inclusion.

12. Significance

Overall, this study will contribute to the knowledge of the effects of cognitive training on cognition in patients with AD in the prodromal to moderate stages. The comparison of results obtained for neuropsychological tests, questionnaires, and experimental tasks by REG patients with those obtained by MFG patients will inform about the effects of cognitive training at home carried out in addition to training in SLT office. This will provide clear indications about the usefulness of this type of cognitive training programme for patients with AD. The comparison of the results obtained by MFG patients with those obtained by HFG patients will provide indications as to the best frequency of training sessions needed.

Beyond the benefits of cognitive training on patients with AD cognition, and the importance of trying to determine the best frequency for optimal effects, other issues, which are independent of the cognitive training programme, may impact on its success if not carefully considered. AD has an important impact on autonomy, emotional balance and motivation, which are often linked to self-esteem [19-21]. Thus, it seems important, when designing cognitive training protocols for patients with AD to take into account psychological, environmental and autonomy factors for a more optimal cognitive training plan, which aims at the well-being of the individual as a whole [21,50-27]. Through the questionnaires administered in our protocol [32-37], we hope to shed light on the emotional benefits of training and answer questions regarding the engagement and adherence in patients with AD, as well as to provide a more informed opinion on the importance of seeking third-party help. Understanding whether the same issues of training independence arise for patients with mild and moderate AD will allow us to develop more accurate computer-based home training protocols for different patient profiles. These protocols should take into account the severity of cognitive decline

which may affect training autonomy as cognitive impairment increases. These considerations will allow us to consider solutions for less autonomous people.

Authors Contribution

Author Contributions: Conceptualization, S.D. and H.C.; Data treatment, S.D.; Project administration, S.D. and H.C., Supervision, H.C., F.T-B., B.C.; Writing—Original draft, S.D. and H.C.; Writing—Review & editing, S.D., H.C., F.T-B. and B.C. All authors have read and agreed to the submitted version of the manuscript.

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Competing interests' statement

Franck Tarpin-Bernard and Bernard Croisile are cofounders and shareholders of SBT Humans Matter.

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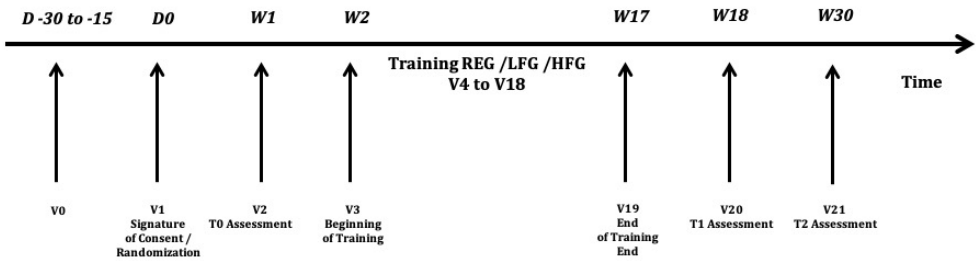

Figure 1: illustrating on the time axis the evolution of the experiment with the facts marked on a weekly basis trainings take place between the 2nd and the 17th week for the 3 training groups simultaneously. Note: V = Visit; W = Week; D = Day; T = Time of assessment; REG = regular group; HFG = high frequency group; MHG = moderate frequency group.

321x118mm (72 x 72 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	7
Protocol version	#3	Date and version identifier	5
Funding	#4	Sources and types of financial, material, and other support	19
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1;19

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	n/a
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	6

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-9
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n/a

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5-6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7-9; 11
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	13
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	13
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	13
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13-14
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	19
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a