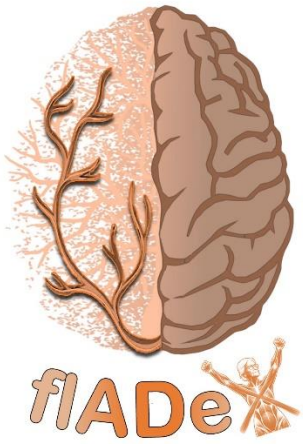

Manual of Procedures FLADEX project

MOP Chapter 3: Recruitment, eligibility and screening

Chapter 3. Recruitment, eligibility and screening

Index

1. Introduction:

In this MOP chapter, we aim to explain the participant **recruitment process,** outline the **inclusion and exclusion criteria** (Eligibility), and describe the procedures for conducting the **phone interview** within the flADex study.

2. Recruitment:

The target for the flADex study is to recruit **20 individuals (10 men and 10 women)** aged 68-83**,** who completed the **AGUEDA trial** and met the additional eligibility criteria defined for the flADex study (see 3.0 Eligibility criteria). Recruitment will be conducted via telephone by directly calling participants. Eligible participants will be contacted for recruitment in the following order:

I. Participants **under 72 years old*** who have **responded positively** to the **AGUEDA post-study questionnaire**, expressing the intention to participate in another study related to the AGUEDA study.
II. Participants **under 72 years old*** who have **responded negatively** to the **AGUEDA post-study questionnaire**, stating the decision not to participate in another study connected with AGUEDA.
III. Participants **aged 72 or older*** who have **responded positively** to the **AGUEDA post-study questionnaire**, indicating the willingness to participate in another study connected with AGUEDA.
IV. Participants **aged 72 or older*** who have **responded negatively to the AGUEDA post-study questionnaire**, declaring the choice not to participate in another study connected with AGUEDA.

***Note: The age requisite refers to the participant's age at the time they started their participation in the AGUEDA study. This corresponds to under/over 75 years at the entry in the fladex study.**

The recruitment manager in this study is Beatriz Fernández Gámez. The list of eligible participants in the contacting order and their telephone contacts will be available through the Redcap tool in the phone screening section. The screening process will be performed as follows:

I. The initial phone screening will take place two months before the project begins to pre-recruit the 20 potential participants (by the end of July 2024).
II. As the initial familiarization session approaches (end of September 2024), participants will be called to confirm their participation. Note: if a participant declines during this second call, the recruitment manager will need to contact another participant to replace them.
III. Additionally, if any participant drops out or quit the study at any stage for any reason, another participant will be contacted to replace until we have 20 participants who have completed the full study.

3. Eligibility criteria

The eligibility criteria for the flADex study defined below (Table 2) will be checked in two phases, pre-screening phase and phone-screening phase.

3.1 Pre-screening phase:

Participants who completed the AGUEDA trial, and therefore met all the eligibility criteria defined for the AGUEDA study at the beginning of the study (see table1, (Solis-Urra et al., 2023)) will be considered for screening on the flADex study (Figure 1). Among completers from the AGUEDA trial (n=80), only participants who meet two main inclusion criteria will be initially eligible for the flADex study:

(i) **APOEe4 negative status**.

(ii) **Non-pathological cerebral beta-amyloid status** (based on Centiloid cut-point <12 measured by PET)

These participants (n=54) will be included in the Redcap list in the defined contacting order to check additional eligibility criteria in the phone screening phase.

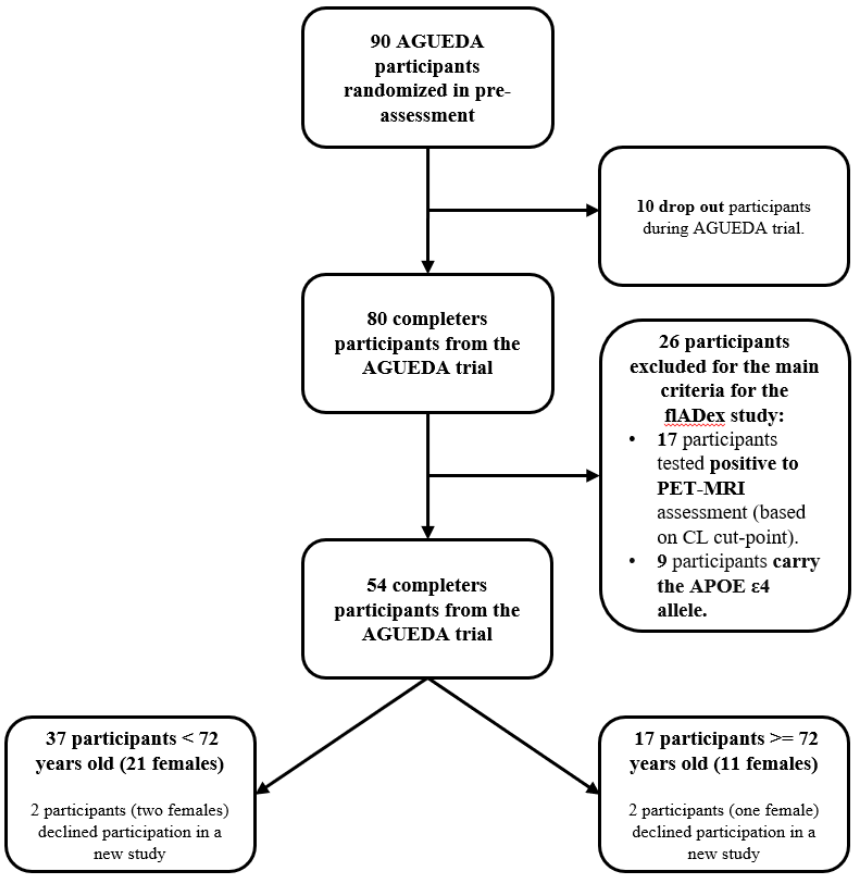

Figure 1. Flowchart for participants initially eligible for the flADex trial.

The basic characteristics for the initially eligible participants from the pre-screening phase for the flADex study are presented in Table 1.

Table 1. Eligible participant characteristics.

Eligible participants < 72 years old			
Characteristic	All n=37	Females n=21	Males n=16
Age (Years)	68.62 (1.86)	68.53 (1.94)	68.75 (1.81)
Cerebral beta-amyloid (CL units)	-3.35 (8.18)	-2.15 (9.57)	-4.93 (5.83)
Declined participation in a new study	2	2	0
Eligible participants >= 72 years old			
Characteristic	All n=17	Females n=11	Males n=6
Age (Years)	75.70 (2.26)	76.24 (2.51)	74.72 (1.37)
Cerebral beta-amyloid (CL units)	-4.68 (10.05)	-5.92 (10.91)	-2.39 (8.68)
Declined participation in a new study	2	1	1

3.2 Phone screening phase:

Additional exclusion criteria for the flADex trial, which will be screened during the phone screening, are detailed below:

(i) Ambulatory with pain or regular use of an assisted walking device.
(ii) Pathological diagnosis related to physical or mental condition.
(iii) No living in community settings during the study.
(iv) MRI incompatibility.

All the inclusion and exclusion criteria for the flADex trial are detailed in Table 2.

Table 2. Summary of the inclusion and exclusion criteria for eligible participants of flADex study.

Inclusion criteria	**Exclusion criteria**
• **No APOE4 carriers:** participants who do not have been identified as carriers of APOE4 through blood sample analysis. • **Negative at cerebral beta-amyloid assessment.** Measured by PET based on Centiloid cut point < 12.	• Ambulatory with pain or regular use of an assisted walking device. • Pathological diagnosis related to physical or mental condition. • No living in community settings during the study. • MRI incompatibility.

4. Phone screening

Researchers in charge of contacting the eligible participants will call each potential participant one by one. They will begin by providing a general explanation of the study and inviting the person to participate. Then, they will **carefully verify** (through the Redcap instrument) whether the participant has reported any **serious incidents** and/or if he/she has been diagnosed with a **serious disease**. Additionally, they must ensure that the participant is **able to move independently and perform moderate exercise**. Finally, the researcher must confirm that **their compatibility for magnetic resonance examination (MRI) has not changed** since the end of their participation in the AGUEDA study. The interviewer will read a **pre-prepared text available on Redcap** (phone screening form). The script reads as follows:

Hello, my name is [Your Name]. I'm calling from the University of Granada, representing the FLADEX project. May I speak with [Potential Participant's Name], please?

I'm calling because we are starting a new study on physical exercise for people who have previously participated in the AGUEDA project and have expressed interest in participating in another related project. I would like to provide you with more information about the research study, and if you're still interested, ask you some questions. Do you have time to talk now? May I have your permission to explain the project to you? Feel free to interrupt with any questions.

The FLADEX study aims to investigate the effects of acute physical exercise on cerebral blood flow for the prevention of Alzheimer's disease. This research, conducted through the University of Granada, focuses on understanding brain function in older adults.

Physical activity has shown benefits in various aspects of physical and mental well-being. In particular, this study explores whether physical exercise has a positive impact on the brain health of older adults. Interested individuals should attend a total of 4 days. The initial session takes place at the iMUDS university building, where the project will be explained in detail. During this session, participants will have the opportunity to review and sign the information sheet and the informed consent form, as well as answer some questionnaires and become familiar with the exercise to be performed.

Subsequently, eligible participants will need to attend the CIMCYC university building once a week for 3 weeks, where the study procedures will be conducted. If you have any questions or need further clarification, please don't hesitate to ask.

During the 3 appointments at CIMCYC, the following tests will be performed:

2 Questionnaires (5 minutes each)

2 Magnetic Resonance Imaging (MRI) sessions (20 minutes each)

2 cognitive testing sessions (15 minutes each)

Exercise or rest condition (30 minutes)

4 blood extractions via only 2 pricks (1 before the intervention and 3 others after the control/exercise condition, separated by 30 minutes each).

Is everything clear? Do you have any questions about any aspect? If there are no questions, I will ask you for some information to confirm your eligibility: Are you interested in participating?

Questions about health conditions since the end of the AGUEDA project:

All the questions I'm about to ask you now refer to the period since you completed the AGUEDA project until today, okay?

- *Have you been diagnosed with any of the following diseases: Parkinson's, Dementia, Multiple Sclerosis, or any brain condition such as stroke, brain injury, or other cerebral damage that required hospitalization (trauma)?*
- *Have you been diagnosed with a condition involving hallucinations or mania such as schizophrenia, psychotic episodes, or bipolar disorder?*
- *Have you visited a psychiatrist in the past year for any illness? (e.g., depression, schizophrenia, various mental disorders)?*
- *Are you currently taking any medication for a psychiatric disorder? (e.g., depression)*
- *Are you currently receiving treatment for Cancer or have you received treatment for Cancer in the past 2 years?*
- *Have you experienced a heart attack (myocardial infarction) or undergone major heart surgery (involving the placement of a stent) in the past year?*
- *Have you experienced any disease involving chronic inflammation in the past year? (Not exclusive, just for reporting purposes)*
- *Have you been diagnosed with Type II Diabetes?*
- *Do you require Insulin to control your diabetes? (injection)*
- *Have you been diagnosed with any other diseases or conditions that may make it difficult for you to participate in the FLADEX project? (Please indicate which ones and if you are currently undergoing treatment/medication)*
- *Is there any reason that prevents you from lying properly inside the MRI scanner, lying on your back with your head/neck aligned with your spine without turning your neck? For example: if you have vertigo, dizziness when lying flat, cervical problems, etc.*

Compatibility questions with MRI since the end of the AGUEDA project:

- *Do you have a cardiac pacemaker, aneurysm clip, implanted cardioversion defibrillator, metal heart valve, other implant or electronic device, magnetically activated implant or device, or neurostimulator?*
- *Do you have any metal in your body such as plates, rods, pins, or stents? Have you had any implants in your eyes (e.g., cataract surgery)?*
- *Have you suffered any injuries where metal had to be removed, such as a bullet?*
- *Have you had joint replacement surgery?*
- *Do you have dental implants, retainers, or plates?*
- *Do you have a history of working with metal such as being a welder or a history of metal fragments in the eye?*
- *Have you had any tattoos on your body in the last 3 months?*

(report responses or other comments in RedCap).

- *Do you need assistance from a walker or any device for walking?*
- *Any other comments regarding the participant's level of physical activity?*
- *Do you have any issues with any of the tests that will be conducted at CYMCIC that I mentioned before? (blood extraction, cognitive tests, MRI, or others)?*
- *Can you confirm your phone number?*
- *Are you available to attend the assessments (at CIMCYC) on Monday, Wednesday, and Thursday for these 3 weeks (one day per week) between 8:00 AM and 1:00 PM?*
- *Are you currently participating in another research study?*
- *Are you eligible to attend the PRE-Screening?*

If the participant is eligible and has confirmed their availability, provide them with an appointment for the familiarization session at iMUDS where the project will be explained in detail and consent will be obtained (also note it in the FLADEX calendar).

If they are not eligible, explain the reasons and ask for as much information as possible, which will be reported in the text box in RedCap.

IN SPANISH:

Hola, mi nombre es [Tu Nombre]. La llamo desde la Universidad de Granada, representando el proyecto FLADEX. ¿Puedo hablar con [Nombre del posible participante], por favor?

La estoy llamando porque empezaremos un nuevo estudio sobre ejercicio físico para personas que han participado previamente en el proyecto AGUEDA y han expresado interés en participar en otro proyecto relacionado. Me gustaría proporcionarle más información sobre el estudio de investigación y, si aún está interesado/a, hacerle algunas preguntas. ¿Tiene tiempo para hablar ahora? ¿Puedo tener su permiso para explicarle el proyecto? Siéntete libre de interrumpir con cualquier pregunta.

El estudio FLADEX tiene como objetivo investigar los efectos del ejercicio físico agudo en el flujo sanguíneo cerebral para la prevención de la enfermedad de Alzheimer. Esta investigación, realizada a través de la Universidad de Granada, se centra en comprender la función cerebral en adultos mayores.

La actividad física ha mostrado beneficios en diversos aspectos del bienestar físico y mental. En particular, este estudio explora si el ejercicio físico tiene un impacto positivo en la salud cerebral de los adultos mayores. Las personas interesadas deben asistir un total de 4 días. La sesión inicial se realiza en el edificio universitario iMUDS, donde se explicará detalladamente el proyecto. Durante esta sesión, los participantes tendrán la oportunidad de revisar y firmar la hoja de información y el formulario de consentimiento informado, así como de contestar a algunos cuestionarios y familiarizarse con el ejercicio a realizar.

Posteriormente, los participantes elegibles deberán asistir al edificio universitario CIMCYC una vez por semana durante 3 semanas, donde se llevarán a cabo los procedimientos del estudio. Si tiene alguna pregunta o necesita más clarificaciones, no dude en preguntar.

Durante las 3 citas en el CIMCYC, se realizarán las siguientes pruebas:

- 2 Cuestionarios (de 5 minutos cada uno)
- 2 sesiones de Resonancia Magnética (MRI) (de 20 minutos cada uno)
- 2 sesiones de pruebas cognitivas (de 15 minutos cada uno)
- condición de ejercicio o descanso (de 30 minutos)
- 4 extracciones de sangre a través de solo 2 pinchazos (1 antes de la intervención y otras 3 después de la condición de control/ejercicio, separadas por30 minutos una de la otra).
¿Está todo claro? ¿tiene alguna duda sobre cualquier aspecto?
Si no hay duda voy a preguntarle unas informaciones para confirmar su elegibilidad:
Estaría interesad@ en participar?

Preguntas sobre condiciones de salud desde el fin del proyecto AGUEDA:

Todas las preguntas que voy a hacerle ahora se refieren al periodo que ha pasado desde que usted ha finalizado el proyecto AGUEDA hasta el día de hoy, ¿vale?

- *Ha sido diagnosticad@ con alguna de las siguientes enfermedades: Parkinson, Demencia, Esclerosis Múltiple, ¿o cualquier condición cerebral como: ictus, infarto u otro daño cerebral para que has tenido que ir al hospital (traumas)?*
- *Ha sido diagnosticad@ de una condición donde tuviera alucinaciones o mana como esquizofrenia, brotes psicóticos o trastorno bipolar?*
- *ha visitado al psiquiatra en el último año por alguna enfermedad? (por ejemplo, depresión, esquizofrenia, distintos trastornos mentales)?*
- *¿Está tomando actualmente algún medicamento para algún trastorno psiquiátrico? (por ejemplo, depresión)*
- *¿Está actualmente recibiendo tratamiento contra el Cáncer o ha recibido tratamiento contra la enfermedad del Cáncer en los últimos 2 años?*
- *¿en el último año sufrió algún ataque al corazón (infarto de miocardio) o se sometió a una cirugía mayor de corazón (implicando la colocación de un stunt)?*
- *¿en el último año sufrió alguna enfermedad que genere inflamación crónica? (no excluyente, solo para reportar la información)*
- *Ha sido diagnosticad@ con Diabetes tipo II?*
- *¿Necesita Insulina para controlar su diabetes? (inyección)*
- *Ha sido diagnosticad@ de otras enfermedades o condiciones que le dificulte ser parte del proyecto FLADEX? (Indique cuales y si está tomando tratamiento/medicación).*
- *Existe algún motivo que no le permita colocarse debidamente dentro de la resonancia, tumbado hacia arriba con la cabeza/cuello alineado con la columna sin girar el cuello? Ej: si tiene vértigo, o mareos al tumbarse en plano, problema cervicales ecc..*

Preguntas de compatibilidad con MRI desde el fin del proyecto AGUEDA:

- *¿Tiene marcapasos cardíaco, aneurisma clip, desfibrilador cardioversión implantado, válvula cardiaca metálica, otro implante o dispositivo electrónico, implante o dispositivo activado magnéticamente o neuro estimulador?*
- *¿Tiene algún metal en tu cuerpo como placas, varillas, alfileres o stents? ¿Ha tenido algún implante en sus ojos (por ejemplo, cirugía de cataratas)?*
- *¿Ha sufrido alguna lesión en las que tuvieran que retirarle algún tipo de metal como una bala?*
- *¿Ha tenido una cirugía de reemplazo articular?*
- *¿Tiene implantes dentales, retenedores o placas?*
- *¿Tiene antecedentes de trabajar con metal como un soldador o un historial de fragmentos de metal en el ojo?*
- *¿Se ha realizado algún tatuaje en su cuerpo en los últimos 3 meses?*

(reportar las respuestas u otros comentarios en el RedCap).

- *¿Necesitas de ayuda de un andador o cualquier dispositivo para caminar?*
- *otros comentarios respeto al nivel de actividad física del participante?*
- *usted tiene algún problema con una (o más) prueba que se le harán en el CYMCIC y que le dije antes? (extracción de sangre, test cognitivos, resonancia u otras)?*
- *me puede confirmar su número de teléfono?*
- *¿Tiene disponibilidad a asistir a las evaluaciones (en Cimcyc) el lunes, miércoles y jueves durante estas 3 semanas (un único día a la semana) entre las 8:00 y las 13:00?*
- *¿Estás actualmente participando en otro estudio de investigación?*
- *¿Es elegible para acudir al PRE-Screening?*

Si el participante es elegible y ha confirmado su disponibilidad, darle cita para la sesión de familiarización en iMUDS donde se le explicara el proyecto en detalle y firmar el consentimiento (apuntarlo también en el calendario de Fladex).

Si no es elegibles, explicar las razones y preguntar más informaciones posibles que se reportaran en la caja de texto que hay en el RedCap.

5. References:

Solis-Urra, P., Molina-Hidalgo, C., García-Rivero, Y., Costa-Rodriguez, C., Mora-Gonzalez, J., Fernandez-Gamez, B., Olvera-Rojas, M., Coca-Pulido, A., Toval, A., Bellón, D., Sclafani, A., Martín-Fuentes, I., Triviño-Ibañez, E. M., de Teresa, C., Huang, H., Grove, G., Hillman, C. H., Kramer, A. F., Catena, A., … Esteban-Cornejo, I. (2023). Active Gains in brain Using Exercise During Aging (AGUEDA): protocol for a randomized controlled trial. *Frontiers in Human Neuroscience*, *17*, 1168549. https://doi.org/10.3389/FNHUM.2023.1168549/BIBTEX