



RESEARCH PROJECT DESIGN

Title: Clinical, demographic and genetic factors associated with response to computer-assisted cognitive stimulation treatment as part of non-pharmacological care in patients with delirium. Feasibility study.

Version: 30/01/2026

ABSTRACT (Aims and methodology)

The objectives of our study are to determine whether it is feasible to use a computer-assisted cognitive intervention for patients with delirium by occupational therapists, over a period of one week, in addition to the usual non-pharmacological interventions, compared to the usual non-pharmacological interventions alone, specifying the completion of tasks and the difficulties encountered. It also aims to determine the degree of response in relation to the presence and severity of delirium and its symptoms, which individual and grouped symptoms respond best, and how different genetic factors, other biomarkers, clinical and demographic factors affect the onset of delirium and the response to these interventions. Participation in the study will be offered to patients admitted to the subacute care centre who are 60 years of age or older and do not have severe communication or sensory difficulties. They will be assessed within the first 24-48 hours to obtain a provisional diagnosis of delirium using the DDT-pro scale, which will then be confirmed according to DSM-5 criteria, and the severity of their symptoms will be determined using the DRS-R98 scale. Patients without delirium will serve as a control group for biomarker studies and will receive usual care. Patients with delirium will be randomly assigned to two groups; both will receive non-pharmacological interventions focused on the sleep-wake cycle, cognition, and active mobilisation, and one group will also receive specific cognitive stimulation exercises using online software on a tablet. After one week, the presence and severity of delirium will be reassessed using the DDT-Pro and DRS-R98 scales and DSM-5 criteria. Baseline demographic, clinical, laboratory, and genetic data will be collected from all participants to determine their influence on the presence, characteristics, and course of delirium.

EXPECTED RESULTS

We expect to demonstrate that delirium improves with the most validated non-pharmacological measures to date, but that it responds better when a specific computer-assisted cognitive therapy is included. Improvement will be measured in terms of overall delirium severity and its individual symptoms after one week of treatment.

The specific symptoms of the delirium episode, other clinical characteristics of the patient and the genetic background will influence the response to treatment. We will be able to collect clinical, demographic, genetic and other biomarker data from patients with and without delirium.

COMMUNICATION AND DISSEMINATION PLAN

The results obtained will be disseminated through a scientific article and at conferences where the non-pharmacological management of delirium in hospitalised patients with heterogeneous pathology may be of interest. Similarly, the results will be disseminated to the centre's care team to promote care changes through talks, intranet news, clinical sessions and via social media aimed at the general public.



POTENTIAL IMPACT

- Improvement of human resources, equipment or infrastructure: will allow for the more accurate and effective organisation of the patient's rehabilitative treatment.
- Improvement in knowledge: will allow for a deeper understanding of the clinical presentation, effective treatments and factors associated with delirium.
- Translation or application of knowledge: will allow us to determine whether a computer-assisted therapy is feasible and useful in treatment, and in which subtypes of delirium it may be most effective.
- Health improvement and social impact: The aim is to enhance the care team's intervention in the patient's recovery and thus return them to their social situation, that is, to minimise the socioeconomic impact of the acute episode.
- Economic impact (technology transfer, commercialisation, ...): To identify which technologies may be useful in the treatment of delirium and, specifically, in which subtypes (based on symptoms, other clinical parameters, demographics and/or associated biomarkers) could allow the development of knowledge transfer products in the future.



BACKGROUND AND CURRENT STATUS OF THE TOPIC

Delirium

Delirium is characterised by an alteration of consciousness and, therefore, of all higher mental functions, which distinguishes it from coma, in which there is a total state of unconsciousness (1). Phenomenological studies of delirium have identified three groups of core symptoms that allow delirium to be differentiated from pathologies with which it may share symptoms, such as dementia (2). The three core domains of delirium are: the cognitive (which comprises attention, orientation, short- and long-term memory, and visuospatial ability), the circadian (the sleep-wake cycle and motor activity), and higher-order thinking (language and the course of thought)(3). It is also assumed that there is a triggering cause for the episode, which, once corrected, would lead to a complete or partial remission of the delirium's symptoms.

Delirium is highly prevalent across various clinical settings, particularly when risk factors such as advanced age and dementia are present. Specifically, at the Monterols Postacute Care Centre we have found prevalence rates of around 30%. In addition to being a prevalent phenomenon, experiencing an episode of delirium has been associated with various unfavourable patient outcomes, such as increased length of hospitalisation, cognitive decline, risk of dementia and higher mortality (4).

Cognition and delirium

There is evidence of a bidirectional relationship between delirium and cognitive impairment. Experiencing delirium increases the risk of subsequently developing cognitive impairment and dementia (4,5), and the presence of dementia is also the most frequently associated factor with the onset of delirium, in various clinical settings (6). In addition to global cognitive impairment (7), alterations in specific cognitive functions have also been associated with an increased risk of delirium, particularly disturbances in orientation and executive functions (motor and constructive) (8,9). In people without dementia, alterations in attention and language are also associated with the risk of delirium (9, 10). Other factors, such as the type of clinical service, the causal aetiological factors of delirium or the type of delirium (hypo- or hyperactive, for example) can influence the degree and type of cognitive functions associated with the risk of developing delirium (11).

Risk factors for delirium

Genetics of delirium: genetic factors, such as carrying the APOE4 genotype, increase the risk of delirium, as well as its greater duration and severity compared to non-carriers, both in the post-operative setting and in post-acute care for patients with dementia (12-15). However, genetic studies are heterogeneous. The most investigated gene is APOE, but although many studies suggest a relationship with the presence or progression of delirium, the results of the latest meta-analyses are negative (14), probably due to study heterogeneity and the still small number of participants included. More studies with larger samples are also needed to understand the interactions between different genes, with other biological factors and with specific phenotypic characteristics of delirium (14).

Genetics of cognition: cognition is a complex process influenced by genetic and environmental factors. A whole-genome study, however, found that educational attainment was clearly associated with common SNPs, mainly in regions that regulate gene expression in the foetal brain (16). These associations implicate potential biological pathways that could serve as a basis for understanding the genetic factors associated with neurocognitive diseases.



Inflammation: The inflammatory process and oxidative stress have been associated with the onset of delirium in older people (17), where different markers such as C-Reactive Protein (CRP), Interleukins 6 (IL-6) and IL-8, IL-10 and IGF-1 have been associated with an elevated risk of developing post-surgical delirium (18)

Nutritional deficits: Low blood levels of vitamin B12 and vitamin D have also been shown in some studies to be associated with the onset of delirium (19). Studies are scarce, most focusing on the risk of delirium onset rather than its progression, and they do not always take into account the potential association between different biological and clinical factors.

Triggers of delirium

In addition to the causes that predispose individuals to delirium, this syndrome is characterised by being triggered by one or more factors that precipitate the episode. The number and severity of factors required to trigger an episode of delirium will depend on the individual's underlying vulnerability. These factors can be very diverse and are associated with various pathophysiological mechanisms; The most commonly described complications are related to the surgery type and surgical complications, neurological injuries, anaemia, organ failure, infection, mechanical ventilation, renal injuries, pain, metabolic or electrolyte disturbances, the use or withdrawal of certain drugs (such as benzodiazepines, opiates, neuroleptics, anticholinergics or polypharmacy), urinary catheters, mechanical restraint, prolonged length of stay, ICU admission or sleep disturbances (6).

Prevention and treatment of delirium

Despite the frequency and consequences of delirium, few measures have been shown to be effective in prevention, and even fewer in relation to treatment (20). Non-pharmacological measures have been the most studied, showing that the multi-component approach (described as intervention on more than one risk factor) could reduce the incidence of delirium by up to 43% in hospital units other than the intensive care unit (ICU) (21). However, the preventive efficacy of all non-pharmacological interventions at an individual level is unclear, and the most supportive evidence is in favour of reorientation (including the use of familiar objects), cognitive stimulation and sleep hygiene. At the pharmacological level, no clear efficacy has been demonstrated for any preventive treatment, with the exception of dexmedetomidine when used as an adjunct in preoperative sedation (22).

The cognitive interventions that have been studied are usually part of multi-component interventions with a preventive intent. The cognitive intervention with the most evidence, when analysed individually, is reorientation (21). One study demonstrated that it was feasible for the occupational therapy team to provide cognitive intervention to delirious patients admitted to the ICU, with 20-minute interventions twice daily tailored to the patient's clinical condition; however, due to the small number of participants recruited, it was not possible to analyse the degree of clinical response to this therapy (23).

Regarding the use of digital technologies in delirium prevention, cognitive stimulation exercises via an app have been described, which include interventions in memory, imagination, reasoning, reaction time, attention, processing speed and executive functions, and have been shown to reduce the incidence of post-operative delirium (24) and may be useful in older patients admitted to hospital or intermediate care settings (25), but with no published results yet. We are not aware of



any further studies concerning the use of digital technologies for the prevention or treatment of delirium.

Studies focusing on the treatment of delirium have mainly concentrated on pharmacological interventions, with similarly very varied results and, at present, only some evidence for the use of dexmedetomidine in the ICU to reduce the duration of the episode (22). The few studies on non-pharmacological treatment of delirium yield contradictory results, and, similarly to preventive interventions, only multi-component treatments have shown some positive outcomes, albeit very inconsistent and with high variability of the interventions included in each study (26).

Use of genetic risk (*polygenic risk score*) to predict delirium

Polygenic risk scores are used to explain the relative risk of a disease using data from large-scale genetic studies. Currently, there are no studies to determine the *Polygenic Risk Score* (PRS) for delirium, but there are for other related conditions.

A study showed that genetic risk for Alzheimer's disease increases the risk of developing delirium (27). Also, given the relationship observed between frailty and delirium, another study found that genetic risk for frailty based on GWAS also increases the risk of developing delirium (28). Finally, as we have previously mentioned, a GWAS study indicated that genes expressed preferentially in neural tissue, especially during the prenatal period, are associated with the level of education attained (16).

Proposal

We propose that in patients with delirium on admission, a specific cognitive intervention using digital technology, in addition to multi-component therapy based on improving the sleep-wake cycle, basic cognitive reorientation stimulation and active mobilisation, will allow for a higher rate of delirium improvement after one week of intervention, taking into account the influence of clinical, genetic and demographic factors.



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HYPOTHESIS

Principal:

- A one-week computer-assisted cognitive intervention, delivered by occupational therapists and focusing on attention, orientation, and visuospatial ability, is feasible in patients with delirium and produces greater overall improvement than other non-pharmacological interventions alone.
- Patients with delirium respond differently to non-pharmacological interventions according to the symptoms they present (individually or clustered) and their genetic risk burden for delirium, Alzheimer's type dementia, frailty and educational level.

Secondary:

- Clinical markers such as the potential cause of delirium, medications, the presence of dementia or other comorbidities, are modulators of the response to non-pharmacological therapies for delirium
- Biomarkers of inflammation, anaemia, and levels of vitamins B12 and D are modulators of the efficacy of non-pharmacological measures in the treatment of delirium.
- The APOE genotype and its interaction with clinical and demographic factors influence the onset of delirium, its symptoms and the response to non-pharmacological therapies for delirium.

OBJECTIVES

Primary:

- To determine whether it is feasible for occupational therapists to carry out a computer-assisted cognitive intervention for people with delirium over a week, in relation to whether participants can complete the proposed exercises twice a day and the difficulties faced by therapists.
- To determine whether a computer-assisted cognitive intervention, in addition to usual non-pharmacological interventions (cognitive stimulation, mobilisation and improvement of circadian cycle disturbances), compared with usual non-pharmacological interventions alone, allow for greater improvement in the presence and severity of delirium and its symptoms after one week
- Determine which delirium symptoms, both individual and clustered, respond best to non-pharmacological techniques, particularly specific cognitive therapy using a tablet, and how the genetic risk burden for Alzheimer's-type dementia, frailty and educational level affects this response.

Secondary:

- To determine the demographic and clinical factors that affect the response of patients with delirium to specific non-pharmacological therapies.
- Determine whether routinely obtained biomarkers (inflammatory, anaemia-related, vitamin B12 and D) affect the response of patients with delirium to non-pharmacological therapies.
- Initiate the collection of a clinical and blood data sample that will allow subsequent studies to increase the sample size and delve deeper into the analysis of biomarkers, particularly the APOE genotype, and the interaction between these and other clinical factors in the onset of delirium, its symptoms and response to non-pharmacological therapies.



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METHODOLOGY

a. Study design

Feasibility, experimental, analytical, prospective study

b. Study participants

- **Setting:** The study will be conducted at the Monterols Postacute Care Centre (CAI, in Catalan) in Reus (Spain), which has convalescence, long-stay and psychogeriatric units. Patients requiring post-acute care admitted to the centre are, in most cases, older people, although adults of any age may be admitted.
- **Sample size:** Participants will be those admitted to the Monterols Postacute Care Centre from 15 February to 15 August 2026, who agree to take part in the study and sign the informed consent. It is expected that with the usual admission rate of 7–8 patients per week and a prevalence of delirium on admission described in our unit at 30%, we would have an approximate n of 50 patients with delirium and around 150 without delirium on admission. The sample size of 50 patients with delirium was calculated using a sample-size calculation programme, taking into account that the programme's default power is 80%. An OR of 3 is considered clinically relevant, and it is acceptable to run the risk with this sample size, which has sufficient power for that OR.
- **Criteria**
 - **Inclusion criteria:**
All patients aged 60 years or over who are admitted to the centre between 15 February and 15 August 2026 and who sign the informed consent (the patient and their family or legal guardians if the patient's cognitive condition prevents them from giving consent themselves).
 - **Exclusion criteria:**
Patients who, at the time of admission, meet the criteria for palliative end-of-life care.
Individuals under 60 years of age, to ensure sample homogeneity and reduce confounding factors.
Individuals with severe visual or hearing impairment or aphasia, due to the difficulty of carrying out the cognitive intervention.
Serious communication difficulties due to language.

c. Methods and procedures to be applied

Clinical assessment instruments

The research staff will collect the sociodemographic and clinical data of participants on admission from the medical record: Day of admission, date of birth, age, sex, educational level, marital status, living/residential status, admission diagnoses, use of psychotropic drugs, opiates and anticholinergics, polypharmacy, the need for urinary or venous catheters, presence and severity of dementia (S-IQCODE and GDS scales), depressive symptoms (Cornell scale), the patient's functional status (Barthel, FAC and Tinetti scales, comorbidity (Charlson Comorbidity Index). After one week, the pharmacological changes made will also be recorded, whether the usual general non-pharmacological treatment could be administered, and any relevant clinical events (referral to A&E, death, falls, mechanical restraint, new diagnoses or other significant events).

Biochemistry and haematology

Results of the routine clinical laboratory tests performed at the centre will be obtained. Specifically, haemoglobin, albumin, lymphocytes, neutrophils and ultrasensitive CRP will be used as inflammatory markers, together with vitamins B12 and D.

Biological sample and DNA isolation



A blood sample (10 ml EDTA tube) will be collected and sent to the IISPV Biobank for processing and storage. Plasma will be separated from the cells and DNA isolated from the cells for genetic analysis.

Whole-genome SNP analysis

Genotypes of SNP-type variants will be determined using the Global Diversity Array (Illumina). This analysis will be subcontracted.

Procedure

See Figure 1. Prior to the start of the study, a pilot trial will be conducted to assess the correct administration of the delirium scales (DDT-Pro, DRS-R98 and RADAR) on a random sample of 10 admitted patients and thus agree the assessment criteria among the investigators. Patients involved and their families will be informed about the study to be conducted and invited to evaluate it and propose any modifications they deem appropriate. In the event of any significant changes to the protocol, the Ethics Committee will be duly informed for approval prior to the start of recruitment.

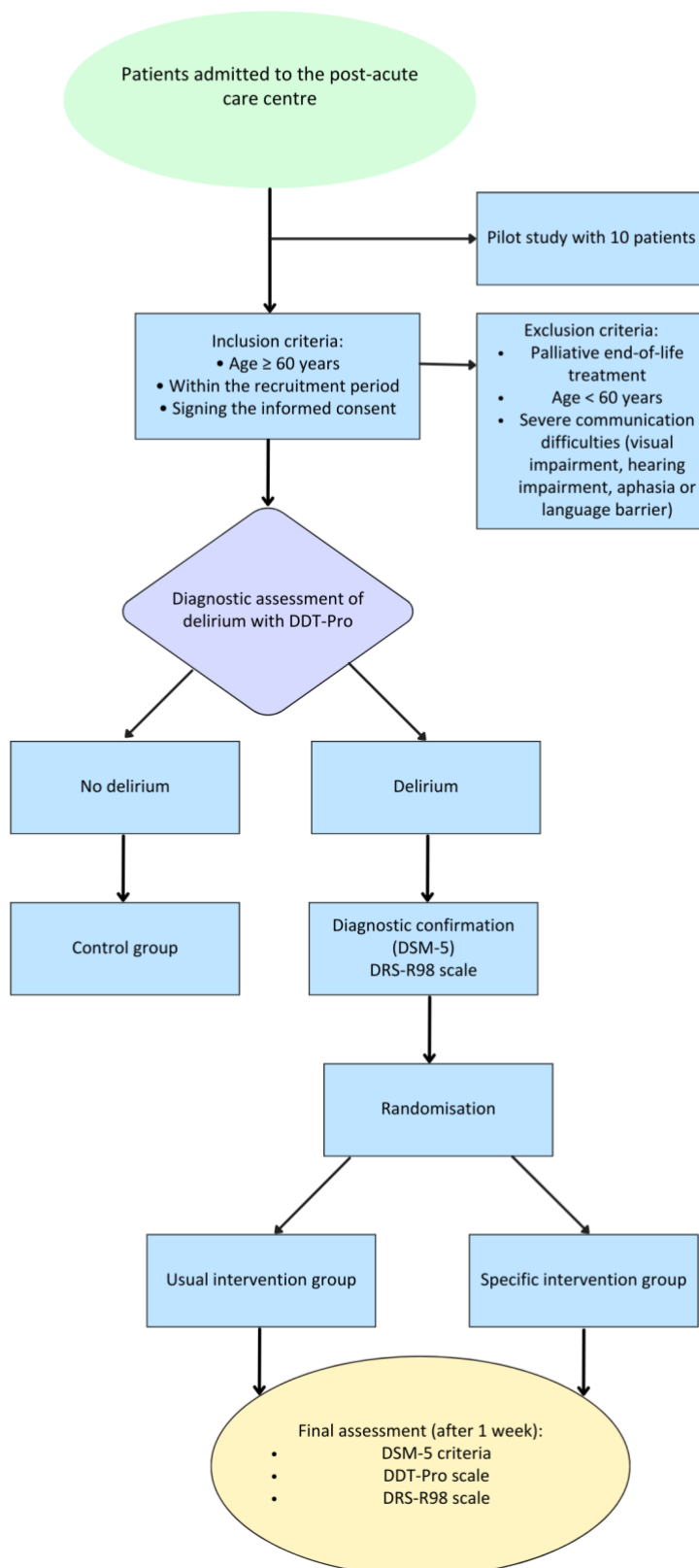
All patients are assessed within the first 24 to 48 hours by family doctors using the DDT-Pro scale, validated at our centre (Sepulveda et al, 2021). DOI: [10.1016/j.genhosppsy.2021.03.010](https://doi.org/10.1016/j.genhosppsy.2021.03.010) with good sensitivity and specificity, and which allows for a provisional diagnosis of delirium and sub-syndromal delirium, measurement of its severity and assessment of its three core domains. Once recruitment has begun, patients with a positive screening for delirium will be assessed by the psychiatrist or the psychiatry resident, who will confirm the diagnosis of delirium according to DSM-5 criteria and the presence and severity of symptoms using the DRS-R98 scale. The DRS-R98 consists of 16 items scored on a Likert scale, allowing the severity of each delirium symptom to be assessed and its three core domains defined. It also distinguishes delirium from subsyndromal delirium and dementia and has been validated in various clinical settings, including the Monterols Postacute Care Unit. (Sepúlveda et al, 2015. DOI: [10.1016/j.psym.2015.03.005](https://doi.org/10.1016/j.psym.2015.03.005) ; Sepulveda et al, 2017. doi: [10.1016/j.dadm.2016.11.002](https://doi.org/10.1016/j.dadm.2016.11.002)). The possible cause or causes of delirium will also be determined using the *Delirium Etiology Checklist*.

All individuals admitted to the centre undergo an admission blood test as part of routine clinical practice on the morning after admission (usually before 7 am); from this test the analytical parameters described above will be obtained. At the same time, from those who have consented to participate, another blood sample (EDTA, 10 ml) will be taken for submission to the biobank for subsequent genetic study.

The entire sample will be divided into two large groups. A first group with no diagnosis of delirium on admission, which will serve as the control group, will receive the usual multidisciplinary interventions according to their clinical needs, at the treating team's discretion. It will also be assessed whether these patients develop incident delirium during the first week of admission, using the screening scale (RADAR), validated in our centre and routinely administered by nursing staff on each shift (Sepulveda et al, 2025). <https://doi.org/10.1016/j.ejpsy.2024.1002729>), with subsequent confirmation by the general practitioners using the DDT-Pro scale. Patients with incident delirium during this first week will be identified as such and will not form part of the control group.



Figure 1. Flowchart of the study participants





The second group will consist of patients diagnosed with delirium on admission. Once the delirium diagnosis has been confirmed, the case manager will randomise these patients using a centrally hosted computer-assisted tool (<https://ctrandomization.cancer.gov/tool/>). Each patient will be assigned to one of two groups:

- **USUAL INTERVENTION GROUP:** Participants will receive a comprehensive geriatric assessment and prescribed a multidisciplinary treatment according to the clinical judgement of the centre's professionals, to address the underlying pathology for which the patient is admitted to the centre and any associated comorbidities. The indications for pharmacological and non-pharmacological delirium management included in the centre's clinical guideline will be followed.

With regard to the non-pharmacological treatment of delirium, specific measures will be taken for:

- a) Orientation and cognitive stimulation tools: Prioritise using the bed next to the window. Encouraging the presence of photos and other familiar objects for the user. Use of calendars and clocks, active reorientation by family and healthcare staff. Visuo-spatial measures to aid the user's orientation within the room or unit. The occupational therapist will be responsible for coordinating these actions.
 - b) Early active mobility: with walking and active mobility groups in the gym. The physiotherapists will be responsible for coordinating these activities.
 - c) Sleep–wake cycle: Respect the night-time rest by adapting the timing of clinical procedures. Educate family members and support auxiliary nursing staff to try to keep the person awake during daytime hours (except for the designated short midday nap). Maintenance of intervention schedules to promote routine. The nursing supervisors will be responsible for coordinating these actions.
- **SPECIFIC INTERVENTION GROUP:** Participants in this group will also receive the treatment determined by the healthcare team for their underlying condition and the non-pharmacological treatment measures described for the usual care group, as detailed in the previous section.

This group will also receive a specific cognitive stimulation intervention using a tablet, administered by the occupational therapist. This intervention will be carried out using the Guttmann online platform, NeuroPersonalTrainer® (GNPT®) (<https://gnpt.es/>), installed on a tablet, so that it can be used in each patient's own room. The intervention will be carried out during the occupational therapists' working hours, with the aim of conducting two interventions each day: one in the morning (approximately between 9:00 a.m. and 1:00 p.m.) and another in the afternoon (between 3:00 p.m. and 4:30 p.m.). Each intervention will have a variable duration, depending on the person's clinical condition, but will not exceed 20 minutes. Each person will receive the intervention for a period of one week from the diagnosis of delirium, which corresponds to five working days.

The GNPT software was initially created for the cognitive telerehabilitation of patients with acquired brain injury (Solana, 2015. DOI: [10.1109/IBHI.2014.2354537](https://doi.org/10.1109/IBHI.2014.2354537)) but has since been shown to be useful in the cognitive rehabilitation of patients with different types of psychosis. The tool allows us to select the interventions we are interested in, and in our



case the same ones will be used for all participants, adjusting the exposure time and difficulty to each individual's condition. We will focus on three cognitive aspects that form part of the core symptomatology of delirium:

- a. Attention: we will base ourselves on sustained attention exercises, such as finding a number in a table or clicking on an intermittent stimulus.
- b. Orientation: based on temporal orientation, with exercises using clocks and calendars.
- c. Visual-spatial ability: exercises will be used based, for example, on maze games or puzzles.

Occupational therapists will assess the delivery of each session, the time at which it is administered, the completion of each of the three cognitive exercises, the reason for any inability to complete them and any other difficulties encountered.

After one week, the presence and symptomatology of delirium will be reassessed using the DTT-Pro scale administered by general practitioners and the DRS-98 by psychiatrists, to determine changes in the clinical manifestations of delirium, as well as whether the patient still meets DSM-5 criteria for delirium. Also, according to the individual symptoms and those grouped by core clusters, it will be possible to carry out a preliminary response analysis specific to each of them.

The general practitioners, the psychiatrist and the psychiatry resident, who will be responsible for the initial and final clinical assessment of patients with delirium, will remain blind to the treatment group allocation. The patients and the staff delivering the specific interventions will not be able to maintain this blinding.

d. Data Management Plan

The personal and clinical data previously described will be collected from the computerised medical record. The personal identifying data are: first names, surname(s) and medical record number, which will subsequently be pseudonymised.

Pseudonymisation will be carried out by assigning a code to each participant, and only the principal investigator and the investigators responsible for data analysis and recording will have access to the coding file.

The investigators will collect the data in paper format, which will be stored in files kept in a locked cupboard to which only the principal investigators have access, in the same way as the informed consent forms, which will be held by the investigator responsible for organising their collection. The data will be transferred to the database created and stored on a dedicated server belonging to the research unit of the University Hospital Institut Pere Mata, designed for this purpose, which can only be accessed with a key held exclusively by the principal investigator and the investigator responsible for data management. The centre and the investigator are responsible for the processing of the data and agree to comply with the current legislation on data protection, which includes Regulation (EU) 2016/679¹ and Spanish Organic Law 3/2018 on Personal Data Protection and Guarantee of Digital Rights

¹ European Parliament and of the Council. General Data Protection Regulation of the EU, Regulation (EU) 2016/679, 27 April 2016.
http://ec.europa.eu/justice/data-protection/reform/files/regulation_oj_en.pdf



The investigator and the centre are required to retain the data collected for the study for a minimum of 10 years after its completion. After this period, the centre will only retain your personal information so that you can receive medical care.

The centre's Data Protection Officer is Josep Pallejà (palleja@peremata.com).

Pseudonymised data may be published open access. Information collected in the study in a pseudonymised form may be used in future medical research projects related to the delirium research line, either at the same centre or in collaboration with other national or international centres. In the event of collaboration with other centres, no personal patient information will be disclosed under any circumstances.

The GNPT software will not be entered with personal data that allows for the identification of the individual, only the code assigned to the study, age and baseline cognitive parameters measured by clinical staff. Likewise, Brainhealth Solutions, S.L. is the company that markets and maintains the GNPT® application or platform. Under no circumstances will Brainhealth Solutions, S.L., as the data processor, use the data for purposes other than maintaining the GNPT® application. The data is held within the territory of the European Union, and the European Union and Spanish data protection regulations apply.

e. Data analysis

- a. The normality of the variables will be tested using the Shapiro-Wilk test; for variables with a normal distribution, parametric tests will be used, and otherwise, non-parametric tests will be employed. The significance threshold will be set at a p-value of 0.05 and will be corrected where necessary using the Benjamini-Hochberg method.
- b. Calculate polygenic risk scores for AD, frailty and educational level, using software such as PRS-cs or PRSice-2.
- c. Intergroup comparisons will be carried out using the ANOVA or T-test for quantitative variables, and the Chi-square or Fisher's exact test for categorical variables. Multivariate logistic or binary regressions will be performed, depending on the variable type, to establish the relationship with variables identified as determinants in the process based on previous analyses.

f. Plan for the management of biological samples

- a. Blood samples will be collected, which will be stored under appropriate security conditions, and it is guaranteed that subjects cannot be identified through means considered reasonable by persons other than those authorised.
- b. The samples are processed and stored in the IISPV Biobank.
- c. During the course of the study, samples may be analysed in laboratories at our centre or in external national or international laboratories, and will be stored in anticipation that any additional analyses related to the study objectives may need to be repeated.
- d. During this process, the person responsible for the samples will be the project investigator.
- e. Once the study has been completed, any remaining samples will be destroyed, unless the participant consents to their storage and use in future research.

g. Ethical aspects

The project has been approved by the Medicines Research Ethics Committee (CEIm) of the *Pere Virgili Health Research Institute* (Ref. 277/2025) and by the Research Commission of the *Pere Mata Institute*. All participants, or their legal representatives where appropriate, sign the Informed Consent Form.

h. Mechanisms to ensure confidentiality

Data are collected using forms designed to facilitate their collection during daily clinical activity, in compliance with the necessary mechanisms to ensure confidentiality. Likewise, the



database is stored in the research unit of the University Hospital Institut Pere Mata, specifically designed for this purpose.

i. Difficulties and limitations of the study

The main limitation of the study will be the limited number of participants. Although we anticipate a sufficient number to determine whether the described interventions produce a significant change in the presence and severity of delirium, it will be difficult to ascertain the influence of these interventions on different subtypes of delirium. The number of participants may prove insufficient for some genetic analyses, and it will be necessary to expand the sample with further studies.

The difficulty of coordinating between professionals with different roles within the centre is acknowledged. Management will be facilitated by the fact that the group regularly works together in the clinical setting and that one person will act as a liaison for all participants.