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Cognitive-enhanced eHealth psychosocial stepped intervention for managing breast cancer-related cognitive impairment: Protocol for a randomized controlled trial

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Abstract

Introduction: Breast cancer often leads to cancer-related cognitive impairment (CRCI), which includes both objective and subjective cognitive deficits. While psychosocial interventions benefit quality of life and distress reduction, their impact on cognitive deficits is uncertain. This study evaluates the integration of a cognitive module into a digital psychosocial intervention for breast cancer patients.

Methods: In this randomized controlled trial (RCT), 88 recently diagnosed breast cancer (BC) patients will receive the ICOnnecta't program (control group) – a digital stepped intervention addressing a variety of psychosocial needs. The experimental group ($n = 88$) will receive ICOnnecta't plus a cognitive module. Assessments at baseline, 3, 6, and 12 months will measure the interventions' impact on cognition, emotional distress, medication adherence, quality of life, post-traumatic stress, work functioning and healthcare experience. Feasibility and cost-utility analyses will also be conducted.

Results: The cognitive module includes three levels. The first level contains a cognitive screening using FACT-Cog Perceived Cognitive Impairment (PCI). Patients with PCI <54 progress to a cognitive psychoeducational campus (Level 2) with content on cognitive education, behavioural strategies and mindfulness. Patients with persistent or worsened PCI (≥6) after 3 months move to Level 3, an online cognitive training through CogniFit software delivered twice a week over 12 weeks.

Conclusions: This study assesses whether integrating a cognitive module into a digital psychosocial intervention improves objective and subjective cognition in breast cancer patients. Secondary outcomes explore cognitive improvement's impact on psychosocial variables. The research will contribute to testing efficacious approaches for detecting and addressing cognitive dysfunction in breast cancer patients.

Trial registration: ClinicalTrials.gov, NCT06103318. Registered 26 October 2023, https://classic.clinicaltrials.gov/ct2/show/NCT06103318?term=serra-blasco&draw=2&rank=4

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Keywords

eHealth, digital health, oncology, women's health, mHealth, wellbeing, digital clinical trials, cancer related cognitive dysfunction, neuropsychology, psycho-oncology

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Contributions to the literature

- The efficacy of a psychosocial intervention in improving cognitive function will provide evidence on the impact of emotional wellbeing on cognitive deficits in breast cancer patients.
- Investigating the benefits of integrating a cognitive module will offer insights into the enhancement of cognitive outcomes through a targeted approach.
- Comprehensive cognitive assessments from the study will clarify which tests more efficiently detect deficits in less time, streamlining the evaluation process.
- Cost-utility and feasibility analysis will support healthcare decision-makers in understanding the individual and social benefits of implementing similar interventions.

Background

Breast cancer (BC) diagnoses have been on the rise, with an increasing number of individuals being affected by this disease.[1,2] However, following treatment advancements, there has also been a significant improvement in BC survival rates. While this is undoubtedly positive news, it brings attention to the issue of quality of life (Qol) for BC survivors.

Many BC survivors face various challenges related to their physical and emotional well-being, which may also include cognitive deficits. These deficits have become so well-established that they now have their own recognized entity in the scientific and healthcare community, referred to as 'cancer-related cognitive impairment' (CRCI). CRCI encompasses a wide range of deficits, including both objective impairments and subjective experiences reported by patients. Objective cognitive impairment refers to measurable deficits in cognitive function, such as memory, attention, language or executive function. When participants suffer from subjective cognitive deficits, it means that they perceive difficulties in cognitive abilities but do not necessarily show objective evidence of impairment on standardized cognitive tests.[3,4] The exact mechanisms through which BC and its treatments lead to cognitive impairment are not entirely understood, as they may be influenced by several individual, illness and/or treatment variables. Some factors that recent meta-analyses have reported to affect objective cognition include chemotherapy agents,[5–8] endocrine therapy,[9,10] inflammatory response[11] as well as stress and psychological factors.[12] Particularly related to stress and psychological factors are subjective cognitive complaints, which have been reported to be affected by depression, anxiety, sleep disturbances, level of education,[13] psychotropic treatments, post-traumatic stress and employment status.[14]

Emerging evidence highlights the potential for improvement in this area, especially of non-pharmacological interventions,[15,16] as patients undergoing chemotherapy are especially reticent to take more medications than strictly needed.[17,18] A recent review[19] explored the efficacy of various behavioural interventions employed for CRCI, identifying which approaches worked best for specific impairments or disturbances. Cognitive behavioural therapies (CBT), cognitive rehabilitation (CReh), and cognitive training (CT) have shown promising results in managing subjective cognition. However, for objective impairments, different techniques demonstrated varying degrees of effectiveness based on the cognitive domain. To address attention issues, meditation or mindfulness interventions proved to be more effective, while CT had a significant impact on managing verbal memory and processing speed, and psychoeducation appeared beneficial for improving executive functioning. Becker et al.[20] showed that BC patients experiencing subjective cognitive impairment also benefited from receiving psychoeducation and discussing the impact of cognitive difficulties on their lives. In this line, a recent retrospective analysis of psychoeducation-based CReh interventions reported a significant improvement in subjective cognition and overall quality of life.[21] Overall, the most widely used techniques to address objective cognitive impairment are CReh and CT, which employ a psychotherapeutic approach with cognitive exercises to improve objective cognition in medical conditions with cognitive deficits.[22] A systematic review involving up to 1124 participants highlighted the effectiveness of CReh for cancer survivors, not only enhancing their subjective and objective cognition but also improving their mood and overall quality of life.[23] The above studies, especially the meta-analysis of Cheng et al.[19] suggests that a one-size-fits-all intervention[24] would not suffice to address all patient needs and potential impairments.

Instead, a comprehensive approach should encompass a variety of strategies to target different cognitive domains and impairments.

In oncological hospitals, despite available treatments, cognitive functioning often goes unnoticed. There are various barriers that make cognitive functioning unnoticed. First, there is a lack of standardized protocols, and second, a lack of awareness from healthcare professionals on the potential impact of breast cancer on cognition and validated interventions. There are also limited resources and time constraints faced by healthcare professionals and, finally, shortage of broad and quick assessments. Recognizing these cognitive deficits is the first challenge in implementing comprehensive care for individuals affected by breast cancer. Efforts have been made in this regard by service providers, improving accessibility and efficiency through cost-effective early and personalized interventions.[25] In this context, information and communication technologies (ICTs) have emerged as a crucial component of eHealth, offering a viable solution to ensure cognitive care for patients with BC.[26,27] Leveraging eHealth can enhance the monitoring of warning signs, facilitate improved communication with healthcare professionals,[28] and provide clinical treatments that are more accessible[29] and cost-efficient compared to traditional modalities.[30] While the potential benefits of eHealth in emotional distress[31,32] and QoL along the cancer journey[33] have been demonstrated, studies assessing eHealth psychosocial interventions which also address cognitive care are scarce.[19]

Considering the complex nature of cognitive challenges experienced by breast cancer survivors, it is urgent to develop interventions that address both objective deficits and subjective cognitive dysfunction in a tailored manner, depending on individual patient needs. This approach will ensure that interventions target the diverse range of cognitive impairments experienced by patients. Leveraging ICTs in eHealth presents a promising avenue to offer accessible clinical interventions, enabling better monitoring and management of cognitive challenges throughout the cancer journey.

The main aims of the current study focus on developing and evaluating the efficacy of the ICOgnition digital intervention in improving subjective cognitive impairment and reducing objective cognitive symptoms in BC patients. The secondary objectives encompass gaining a deeper understanding of cognitive functioning in BC patients within the first year of diagnosis. This includes identifying mediating factors, evaluating the efficacy of online cognitive testing in detecting objective cognitive impairment, and delving into the disparity between objective and subjective deficits. The study will also evaluate the feasibility and cost-utility of the ICOnnecta't and ICOgnition interventions, assessing user's healthcare experience (health literacy, app usability and satisfaction). These analyses aim to provide insights into the scalability and long-term sustainability of the intervention in BC care.

The current study builds upon ICOnnecta't, a Horizon 2020 initiative (ONCOMMUN, https://www.oncommun.eu/) rooted in Responsible Research Innovation Standards and funded by the European Institute of Innovation & Technology. The proposal deployed innovative digital tools in breast cancer psychosocial care, demonstrating a strong commitment to driving advancements in the field. ICOnnecta't emerged to address the unique needs of the BC population while incorporating cutting-edge technological innovations.[34,35] In this sense, a quasi-experimental single-group pilot study was conducted to examine its feasibility, as well as the evolution of psychological outcomes (i.e., emotional distress, social support, post-traumatic stress) in a sample of target patients during it first-year implementation.[32] It was concluded that ICOnnecta't intervention is feasible to implement, showing high rates of intervention acceptance (i.e., the percentage of enrolled patients relative to the eligible patients to whom the program was offered), use and satisfaction with the digital tool among BC survivors.

Considering our previous results experience, the literature reviewed, and the objectives set forth, we hypothesized that the implementation of ICOgnition intervention will be highly feasible. We also anticipate superior results than ICOnnecta't alone at improving subjective and objective cognitive functioning.

Methods/design

Study sample and eligibility criteria

The sample will comprise 176 patients with a diagnosis of BC during the acute survival phase. The inclusion criteria will be:(a) women aged ≥18 and ≤65 years with BC, within 6 weeks after diagnosis, irrespective of prescribed treatment regimen, (b) having online access and a user-level knowledge of the internet and (c) understanding of Spanish language. Exclusion criteria will be: (a) any additional medical condition that may affect neuropsychological performance, (b) presence of a psychiatric condition including substance use disorders in the last 3 months (excluding tobacco addiction), and (c) significant autolytic ideation.

Sample size

Utilizing GLIMMPSE, a web-based tool for sample size determination in the context of General Linear Mixed Models and drawing upon the findings from Bell et al.'s research,[36] we set our significance level (alpha) at 0.05 and our desired statistical power at 0.80 for a two-sided hypothesis test. The expected mean FACT-Cog PCI values per ICOnnecta't group are 41,9 (T0), 33,5 (T1) and 32,6 (T2, T3) and per ICOgnition 38,6 (T0), 23,2 (T1) and 23,4 (T2, T3) with an expected standard deviation

15. Based on these parameters, a total of 176 subjects (88 in each group) are required.

Setting

The trial is conducted at the Catalan Institute of Oncology (ICO, by its initials in the local language) settled in Hospitalet de Llobregat (Spain), a monographic cancer center that started its operations in 1996. The hospital serves as a reference care center in Catalonia. As part of its commitment to BC early detection, ICO Hospitalet invites more than 9400 women each year to undergo BC screening. Around 66% of these women attend the screening unit, resulting in approximately 6200 women receiving mammograms once every two years, beginning at age of 50 and concluding at 69. Furthermore, ICO Hospitalet diagnoses approximately 400 patients with BC every year, highlighting the hospital's significant role in providing care and support to those affected by this condition.

Overview of trial design

The Breast Functional Unit of the ICO Hospitalet will refer the patients with BC who meet the inclusion criteria to the ICOnnecta't Program team. Following this, a health psychologist from the ICOnnecta't program of the Psycho-oncology Service will contact these eligible candidates by call, providing them with a comprehensive explanation of the study and confirming eligibility. Patients accepting participation will then be scheduled an in-person appointment to be included in the trial. At the baseline visit, researchers will explain the study again and obtain informed signed consent. They will then introduce the patient to REDCap, a secure web platform for building and managing online databases and surveys (https://www.project-redcap.org/). Pseudonymization procedures will be followed. Participants will be given a unique code, ensuring that no personal information that could directly identify them will be stored in the system. The study will implement strict confidentiality measures: only the minimum number of authorized research team members will have access to participants' personal information. This approach guarantees the privacy and anonymity of the participants while maintaining the integrity of the research data. The use of REDCap enables secure data collection and ensures the confidentiality of participants' identities.

The study proposes a superiority RCT with two parallel groups (ICOnnecta't vs. ICOgnition, Figure 1). The study design will contain 2 (treatment conditions) × 3 (follow-up assessments) factors. BC patients will undergo random allocation to one of the two treatment arms through REDCap, utilizing simple randomization (1:1). The design will be single-blinded, as both the control group and intervention group will receive active interventions.

The clinician will conduct face-to-face questionnaires with all patients at the beginning (T1) and follow-up (T4). Self-administered measures will be sent via email using

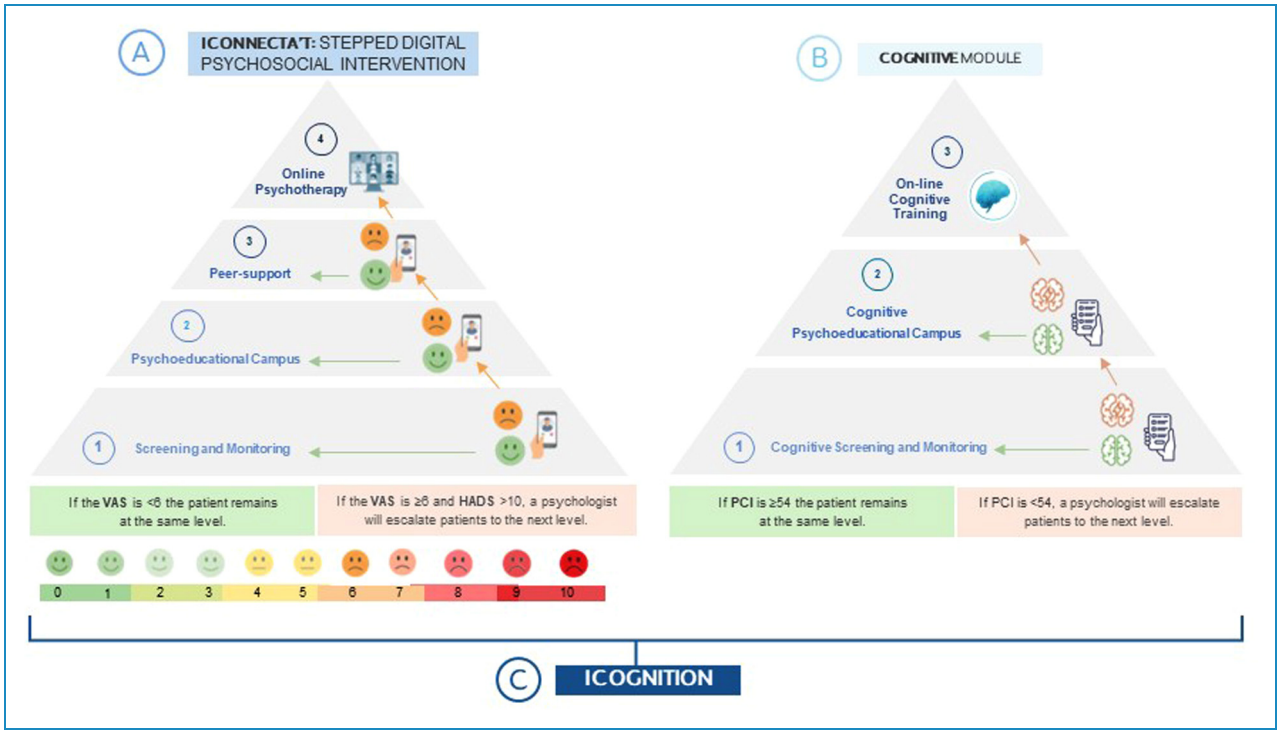

Figure 1. ICOgnition stepped intervention. VAS: Visual Analogue Scale. HADS: Hospital Anxiety and Depression Scale. PCI: Perceived Cognitive Impairment (Subscale of FAST-Cog).

REDCap at T1, T2 (3 months), T3 (6 months) and T4 (12 months). Recruitment will start in April 2024 and last for a year. Table 1 illustrates the eligibility assessment, allocation to study groups and evaluation periods following SPIRIT guidelines.[37]

Ethical considerations

In this randomized controlled trial, the safety and well-being of participants are paramount. Participants are provided comprehensive information, and their informed consent is obtained. Continuous monitoring is in place, and any adverse effects will be promptly addressed. Ethical approval has been obtained from The Technical Secretariat of the Research Ethics Committee of Bellvitge University Hospital (PR270/22) on June 8th, 2023 (Act 14/23). Later, on September 28th, 2023 (Act 22/23), three minor amendments were introduced and approved. The study aims to advance knowledge, while ensuring utmost respect for participants' rights and dignity. Importantly, participants will suffer no harm, as psychosocial and psychoeducational interventions have no known side effects.

Data source

Quantitative data sources. The study protocol collects quantitative data from various sources, encompassing: (a) electronic health records (EHR), (b) demographic, clinical, cognitive and healthcare experience information obtained through online questionnaires using REDCap of the Biostatistical Services of The Bellvitge Biomedical Research Institute (IDIBELL), (c) neuropsychological data gathered during face-to-face study visits at t_1 and t_4, and (4) cognitive data derived from the CogniFit App

Table 1. Schedule of enrollment, interventions and assessments for the ICOgnition trial, following SPIRIT 2013 guidelines.

	Enrollment	Allocation	Post-allocation			Close-out
Timepoint	$-t_1$	0	t_1	t_2	t_3	t_4
Months from Allocation			0	3	6	12
Enrollment						
BC unit eligibility	x					
ICOnnecta't program eligibility assessment	x					
Informed consent		x				
Allocation to study arm		x				
ICOnnecta't/ICOgnition digital onboarding			x			
Interventions						
ICOnnecta't intervention			x	x	x	x
ICOgnition intervention			x	x	x	x
Assessments						
Sociodemographic and clinical variables	x		x	x	x	x
Research questionnaires						
Hospital Anxiety and Depression Scale (HADS)			x	x	x	x
Adherence to Refills and Medication Scale (ARMS-E)			x	x	x	x
FACT-Cog Perceived Cognitive Impairment (FACT-Cog-PCI)			x	x	x	x

(continued)

Table 1. Continued.

	Enrollment	Allocation	Post-allocation			Close-out
EuroQoL-EQ-5D-3L (EQ-5D)			x			x
Post-traumatic Stress Disorder Checklist (PCL-5)			x			x
Work role functioning Questionnaire (WRFQ)			x			x
Healthcare experience outcomes						
Health literacy (VAS 0-10)			x			x
App usability (VAS 0-10)				x		
Intervention Satisfaction (VAS 0-10)				x		
Neuropsychological outcomes						
Rey Auditory Verbal Learning Test (RAVLT)			x			x
Corsi Block-Tapping Test (CBTT)			x			x
Trail Making Test (A and B)			x			x
Verbal Fluency (Spanish Version)			x			x
Digit Span of the WAIS-IV (forward and backward)			x			x
The Stroop Colour and Word Test (SCWT)			x			x
Digit Symbol Substitution Test (DSST; WAIS-IV)						
Chemofog Cognitive Assessment (CogniFit Inc., San Francisco, CA, USA)®			x	x	x	x
Data for cost-utility analysis (psychotropic medication, use of medical care, sick leave, professional salaries, infrastructure costs)			x			x

(Inc., San Francisco, CA, USA). Further data pertaining to the economic evaluation will be detailed below.

EHR comprises information generated during patients' visits to the healthcare system. These records encompass various data domains, such as demographic characteristics, diagnosis codes, dates of diagnosis and treatment, procedures conducted, medications prescribed, visit types and locations, and clinical information provided by health professionals attending to the patient.

Conceptual framework

The study's conceptual framework assesses the efficacy of early stepped interventions for addressing objective and subjective cognitive deficits in individuals with breast cancer (BC). Cognitive training is prioritized for improving verbal memory, processing speed and verbal fluency, while meditation/mindfulness and psychoeducation target attention and executive function, respectively.[19] Psychotherapy interventions are emphasized for subjective cognition due to their efficacy in managing emotional distress.[38–39]

To address personalized assessment challenges in hospitals, the study has created a cognitive module with the same stepped-care approach that ICOnnecta't, for screening, monitoring, and providing resources tailored to cognitive struggles. The integration of ICOnnecta't + the cognitive module is named ICOgnition and will be compared with the psychosocial stepped intervention alone (ICOnnecta't[34]). The study aims to determine the interplay between cognitive deficits (objective and subjective), emotional distress, and work functioning, hypothesizing that early intervention will improve both cognition formats, alleviate distress, and enhance quality of life (QoL). The framework also predicts improved healthcare experience,

particularly in the ICOgnition group, which includes health literacy on cognition and cognitive training, potentially enhancing medication adherence through the expected improvements on memory, attentional functions and mood.[40–42] Furthermore, posttraumatic stress[43] and sleep difficulties[44] are considered control variables as they have been previously linked to cognitive functioning. By integrating efficacious interventions and eHealth expertise, the study aims to optimize cognitive management strategies for cancer patients. Cognitive interventions often incur significant costs, despite their potential for cost-effectiveness[45,46] However, there is a lack for economical evaluation on programs addressed to CRCI in the literature. Existing studies highlight the importance of reducing costs not only for healthcare systems but also for patients.[47] Our study addresses this concern by using a stepped care design. Previous studies have shown that resource-intensive types of care, reserved for patients with persistent problems, have the potential to be cost-effective or even cost-saving.[48,49]

The study's incorporation of interventions based on network meta-analysis findings and the group's expertise in stepped interventions through eHealth strongly suggests that it can offer valuable insights into optimizing cognitive management strategies for breast cancer patients.[50]

Study development and piloting

According to prior mention, the ICOnnecta't psychosocial intervention was examined in a pilot study[32] and a RCT comparing this eHealth intervention versus care as usual (i.e., face-to-face psychosocial intervention) is currently in progress (NCT04372459). These experiences represent a significant strength for the present study as both researchers and health psychologists are well-versed in implementation, participant recruitment and eHealth intervention protocols. It is worth noting that ICOnnecta't showed an acceptance rate of 57.62% among BC survivors; and of these, 74.6% used the digital tool[32] in line with similar eHealth solutions.[51] Thus, a successful recruitment and implementation is anticipated.

Regarding cognitive concern, both the ICOnnecta't single-group pilot study[32] and the RCT in progress only assessed psychological outcomes, such as emotional distress or post-traumatic stress. This aligns with the original intention of the eHealth intervention, which was specifically addressed these problems. Hence, cognitive difficulties in BC patients were neither assessed nor treated.

Building upon this foundation, the current study integrates the cognitive module to incorporate cognitive screening, monitoring and treatment into the existing eHealth psychosocial intervention. Researchers and clinical members of the Psychooncology and Digital Health team of IDIBELL collaborated from January to March 2022 to enhance ICOnnecta't with cognitive care capabilities.

In January 2023, the study received competitive national public funding for its execution (Health Institute Carlos III, PI22/01255). The researchers improved the ICOnnecta't intervention by adding a cognitive module tailored for breast cancer patients' cognitive deficits. They collaborated with ICO's informatics services and partnered with Trilema, the technology provider, to make necessary changes. Changes to the ICOnnecta't platform included adding subjective cognition monitoring and specialized psychoeducational content for cognitive difficulties. The platform was further improved by integrating with the CogniFit App for cognitive assessment and training.

Clinical intervention

The psychosocial stepped intervention, ICOnnecta't (control group). The control group consists of the application of the ICOnnecta't intervention,[32] which is a stepped-care digital intervention provided according to users' psychosocial needs. It comprises four levels staggered by intervention complexity and have achieved acceptance, use, and attrition rates of 57.62%, 74.60%, and 29.66% respectively. Patients will enter the program at level 1 and will be scaled to the next levels according to their needs and complexity, maintaining access to previous steps as they progress. A lead health psychologist specializing in psycho-oncology will guide patients throughout their journey in the stepped intervention (Figure 1, A). Referrals to psycho-oncology, psychiatry or social work departments will be made as needed. Users reported high satisfaction (76.19%) and ease of use (75.95%). A significant majority (94.33%) remained engaged in preventive steps (1st—3rd), briefly explained below.

Level 1: Psychosocial screening and monitoring

This level focuses on screening and monitoring. Patients use a mobile app called ICOnnecta't to assess their emotional distress and physical symptoms. They can communicate their mood through a Visual Analogue Scale (VAS) emotional thermometer of 10 points. If their distress score is high (>5), a video consultation or phone call is scheduled with a health psychologist to evaluate their needs and provide support.[34]

Level 2: Campus: psychoeducation and health education

Level 2 involves accessing ICOnnecta't Campus, an educational platform available through Moodle. Patients can view videos and resources developed by healthcare professionals. The content covers various aspects of breast cancer, including medical information, emotional well-being, personal relationships or healthy habits.[52] Patients spend at least two weeks at this level, and if their distress persists (VAS >5), further assessment is conducted.

Level 3: Community psychosocial support

Consist of a community of psychosocial support through an online platform. Patients can anonymously share concerns, seek advice, share experiences and participate in discussions related to their condition. The platform is supervised by a health psychologist and other members of the oncology team. Patients remain in this level for at least two weeks, and if their distress continues (>5), they advance to the next level.

Level 4: Online group psychotherapy

Online group psychotherapy led by a clinical psychologist specialized in psycho-oncology.

Patients in level 1 can proactively choose to consult educational resources accessing the Campus platform (Level 2) through the ICOnnectát app, even before being scaled to level 2. However, they cannot choose to jump freely from level 2 to 3, or from level 3 to 4 before they are screened into them by a health psychologist.

Cognitive module. The proposed new ecosystem (ICOgnition) complements the ICOnnecta't system with a cognitive module (Figure 1, B) by incorporating screening, monitoring and treatment for cognitive deficits in women with breast cancer. The combined ICOnnecta't + Cognitive module (from now on referred as ICOgnition) will be tailored to each patient's needs. In the case of cognitive monitoring, the criterion for advancing to a more intensive intervention will be the presence of subjective cognitive dysfunction (<54 on FACT-Cog PCI subscale), screened monthly, and/or the presence of objective cognitive disfunction (≤250 in CogniFit Online Assessment), screened every three months. Below, the additional cognitive resources included in ICOgnition intervention are explained:

Level 1: Cognitive screening and monitoring

The first level of the intervention will include a 6-month cognitive screening and monitoring in which patients will be asked to complete the FACT-Cog PCI subscale [40], Version 3, monthly (6 times) and the online objective cognitive assessment (CogniFit) every three months (3 times) (Figure 2). Women with breast cancer who obtain a score of <54[36,53,54] on the PCI subscale or ≤250 (<1SD of the population mean) in the online objective cognitive assessment (CogniFit) at any of these evaluations will be escalated to the 2nd level of the intervention.

Level 2: Cognitive psychoeducational campus

We will enhance the existing campus material on cancer and its treatments[52] by adding ad hoc content related to

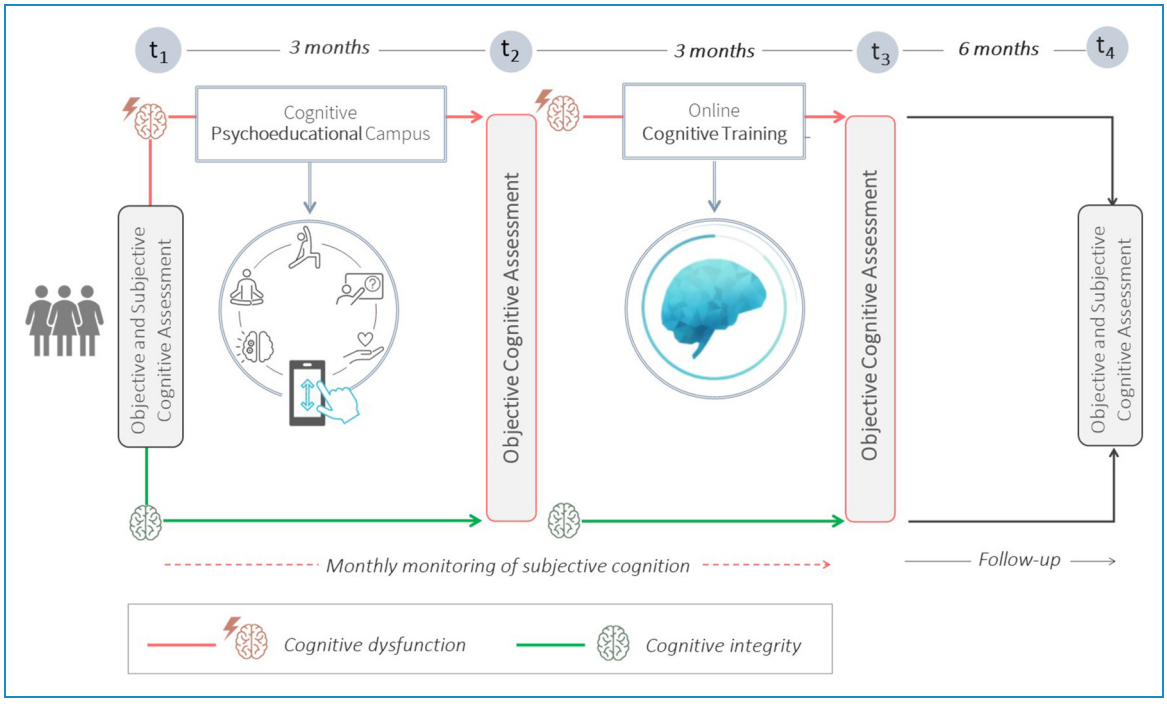

Figure 2. Study protocol for the cognitive module: over the initial 6-month period following study enrollment (T_1), participants will undergo monthly assessments for subjective cognition and evaluations for objective cognition every 3 months (level 1). If any dysfunction is identified in either of these screening assessments, participants will be granted access to the Cognitive Psychoeducational Campus (level 2). If cognitive difficulties persist after joining the Psychoeducational Campus, participants will be moved on to online cognitive training – CogniFit – (level 3).

psychoeducation on cognitive impairment and its management. The new cognitive material will consist of three separate, yet interconnected, blocks.

The first block will focus on cognitive psychoeducation, aiming to improve health literacy and validate symptoms experienced by individuals.[55] The second block will serve as a behavioural guide, offering strategies to enhance cognitive functioning in daily activities.[26] Lastly, the third block will provide strategies to promote embracing cognitive deficits, fostering acceptance and self-compassion through mindfulness and metaphors[56,57] (see more details on Table 2). Mindfulness materials, in addition to the material created by the research team (MSB, ASS, AFV, LCS) will be complemented by audios provided by Dr Garcia Campayo.

Each month, a professional will schedule a call or videocall with the users, considering their preferences. During these sessions, the professional will explain a block and provide an opportunity for users to ask any questions that may have arisen. As the PCI score will be assessed at the end of each month, the effect of each block on subjective cognition will be measured independently.

Once the three blocks have been completed (within approximately three-month timeframe), the PCI score and the online objective cognitive assessment will be reassessed (±1 month). If the scores remain the same or have worsened (6 or more points compared to the initial PCI score[36] or 70 points in the objective online assessment at Level 2 entry (≥1SD)), the patient will progress to Level 3. This assessment process will allow to track the impact of each block on subjective cognitive functioning and the effect of the whole psychoeducational material on objective cognition, to determine the most efficacious strategies for individual patients.

Level 3: online cognitive training

Individual sessions of online computerized cognitive training will be prescribed, with each session lasting 30 min. The training will take place twice a week over a period of 12 weeks. These sessions will be facilitated by the licensed software program CogniFit Inc© 2023,[58] which can be accessed through the mobile application available at https://www.cognifit.com. To ensure seamless integration, the CogniFit program has been integrated with the ICOnnecta't App to ease user experience.

The neurocognitive stimulation program provided by CogniFit consists of a battery of tasks specifically designed to improve cognitive skills based on the user's individual baseline performance. Patients will not need to enter personal information into the application; they'll be automatically directed from the ICOnnecta't App if recommended by a healthcare professional.

Table 2. Campus cognitive resources of the level 2 of the ICOgnition intervention[a].

	Description	Objectives	Content	Format
Block 1	Cognitive psychoeducation What is happening to my cognitive abilities?	To enhance health literacy To normalize and validate their cognitive difficulties	What is cognition and which are the main cognitive domains? Which cognitive deficits may be related to cancer and its treatments? How cognitive deficits can affect the daily functioning	Short videos Infographics
Block 2	Behavioural guide What can I do with the deficits?	To provide tools to informally improve deficits. To provide strategies to compensate cognitive deficits.	Cognitive stimulation strategies that patients can do in their everyday activities. Compensatory strategies How to organize daily activities using and agenda	Short videos Infographics
Block 3	Cognitive resilience Attitude towards the deficit	To promote new attitudes towards the deficit Reduce the emotional distress related to cognitive difficulties	What is mindfulness and which benefits could it have on cognitive deficits? Mindfulness practice with audios[b] Promoting self-compassion Promoting self-acceptance	Short videos Infographics Audios*

[a]Videos available at https://www.psicooncologiaonline.com/publicaciones/

[b]Audios provided with permission of Dr Garcia-Campayo from Zaragoza University (https://www.masterenmindfulness.com/audios-de-mindfulness/).

ICOnnecta't + cognitive module: ICOgnition (experimental group). The ICOgnition intervention combines two distinct components: ICOnnecta't and the Cognitive Module (Figure 1, C). This integrated psychosocial and cognitive intervention allows for a comprehensive intervention strategy that addresses emotional, objective and subjective aspects of women with BC. For instance, individuals may receive psychosocial support when exhibits a distress score exceeding 5 on the Visual Analog Scale (VAS) and be escalated accordingly. Additionally, if their Perceived Cognitive Impairment (PCI) is lower than 54, they will be granted access to the cognitive section of the Campus. Overall, ICOgnition provides a comprehensive and personalized intervention approach to manage breast cancer-related cognitive impairment, addressing both psychosocial and cognitive needs (i.e., patients might be on Level 2 of the psychosocial intervention and in level 3 of the cognitive intervention depending on their needs and evolution to emotional and cognitive measures).

Quantitative evaluation

Outcome measures

Sociodemographic and clinical data regarding cancer characterization will be obtained from two sources: ICO's computerized clinical history system (Patient Care Service, SAP https://www.sap.com/index.html) and semi-structured interviews. Sociodemographic data will include age, city of birth, current city of residence, marital status, educational background, number of children, employment status and any recognized degree of disability. Clinical data will comprise the date of cancer diagnosis, stage of illness, details of oncological treatment, past oncological history and a premorbid estimation of the intelligent quotient will be assessed by means of the vocabulary subtest of the Wechsler Adult Intelligence Scale version-IV (WAIS-IV).[59]

Data will be collected at four times within the clinical trial: baseline, at 3 months at 6 months and at 12 months (Table 1) through the REDCap online data collection platform.

Primary outcomes

Subjective cognition. The main primary outcome is self-reported cognitive function and will be evaluated using the Functional Assessment of Cancer Therapy Cognitive Function version 3 (FACT-COG-v3; https://www.facit.org/measures/FACT-Cog) questionnaire.[60] This tool, comprising 37 items, is extensively utilized in cancer populations and has demonstrated reliable and valid measures.[61,62] It encompasses four subscales: perceived cognitive impairments (PCI), perceived cognitive abilities, impact of PCI on quality of life (QOL), and comments from others on cognitive function. For version 3, FACT-Cog developers recommended using only the perceived cognitive impairment (PCI) sub-scale, widely cited in the literature (https://www.facit.org/facitorg/questionnaires.). PCI scores less than 54 using 18 items has strong discriminatory ability between cancer-related cognitive impairment (CRCI) cases and non-cases.[63] The area under the curve was 0.84 (95% CI = 0.73 to 0.94), indicating good discriminative performance. All PCI items are reversed, meaning that lower scores reflect a poorer perceived performance.

Objective cognition

Paper and pencil tests (composite score). The following cognitive measures have been validated for detecting cognitive difficulties in breast cancer patients, as evidenced in many reviews and meta-analysis.[12,40] Hence, we deem these measures reliable for identifying deficits and changes during monitoring and treatment:

- Verbal learning, immediate verbal memory and delayed verbal memory

  Rey Auditory Verbal Learning Test (RAVLT[65,67]). RAVLT evaluates verbal learning and memory. It involves presenting a list of 15 words to the participant five times and then assessing their ability to recall the words immediately and after a 20-minute delay.In this study, three main variables will be considered: verbal learning through its total score (sum 5 lists), Immediate memory (trial 1) and delayed memory (trial 7, delay recall). RAVLT show acceptable-good reliability rates for its total score (.74) and for delay recall (.88)[66] and is validated in Spanish.[67]
- Visual immediate memory

  Corsi Block-Tapping Tasks: During the Corsi block-tapping tasks, participants are asked to imitate the actions of the researcher. They must tap a series of blocks arranged in a spatial pattern, with each block being tapped in the same order (forward) or in the inverse order (backward) and sequence as demonstrated by the researcher. It assesses visuo-spatial short-term working memory.[68] In this study, the version included is the one comprised in Weschler Memory Scale version III battery (WMS-III[69,70]), with reliability rates of 0.77[71] and validated in the Spanish sample.[72,76]
- Attention

  Trail Making Test (TMT)-A: In this test, participants have to draw a line linking numbers in sequence as fast as possible. It measures cognitive domains such as processing speed or attention[65] and has good reliability for its part A (.76–.89).[75,76]

  Digit Span forward: This test requires to repeat numbers in the same order as read aloud by the examiners and it is one of the main instruments developed to rate auditory attention. The test (forward and backward

forms) was originally designed as of the WAIS-IV[59] and presents a good test-retest reliability (.80).[66]

- Executive functions

  Trail Making Test B (TMT-B): In this part of the test, which measures cognitive flexibility, the patient draws lines to connect the circles in an ascending pattern (like in TMT-A), but with the added task of alternating between the numbers and letters. It is validated in Spanish samples[72,73] and presents reliability rates of 0.86–0.94.[75,76]

  Phonetic fluency: verbal fluency tests involve asking participants to generate as many words as possible that begin with a specific letter within one minute. They show high internal consistency – ($r = .83$) and test-retest correlations tend to be high (above .70[65,66]). The version presented here (PMR) is validated in young[77] and old[74] Spanish adults.

  Stroop Colour and Word Test: This classical neuropsychological test[68] originally developed by Stroop[78] requires participants to name the colour of the word presented, rather than reading the word itself. It assesses cognitive control and inhibition[79] by demanding the suppression of the habitual response (reading) in favour of a less familiar one (naming the colour). Golden (1975)[80] reported reliabilities between .73- .86 for word, colour, and colour-word both for group and individual administration.

- Working memory

  The Digit Span backward task involves the respondent repeating a sequence of numbers in reverse order as presented by the examiners. It serves as a primary instrument for assessing verbal working memory included in the WAIS-IV[59] and exhibits a good test-retest reliability (.80).[66]

- Processing speed

  Digit Symbol Substitution Test (DSST; WAIS-IV): it measures psychomotor performance (D. Wechsler, 2008). This test has high test-retest reliability (.85)[66] and is a valid and sensitive measure of cognitive dysfunction, demonstrating potential as a clinical tool for monitoring treatment effects in disorders affecting cognition.[81]

Digital testing (composite score). The online objective cognitive assessment will be provided by the licensed computer program CogniFit (mobile application, https://www.cognifit.com). CogniFit offers a specific cognitive assessment called 'Chemfog', which measures 6 cognitive domains with acceptable-good-excellent (depending on the domain) internal consistency (mobile) and test-retest reliability: planning (0.77 and 0.83), processing speed (0.77 and 0.76), short-term memory (0.84 and 0.72), focus attention (NA), coordination (0.96 and 0.88) and spatial perception (0.82 and 0.91). Lower scores indicate a poor objective performance in those domains. Scores go from 0 to 800, percentile 25 corresponding to 200, 50 to 400 and 75 to 600.

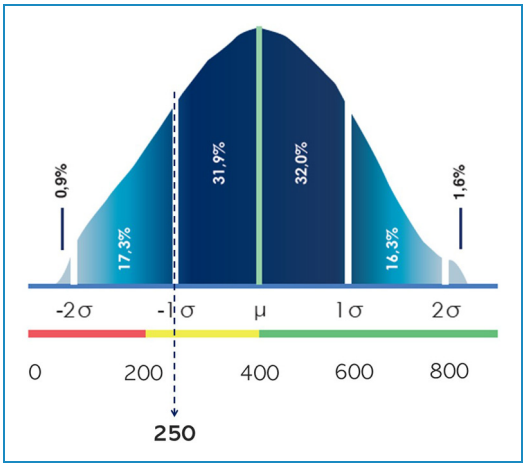

Figure 3. Real distribution of the Cognitive Assessment Battery (CAB) of the CogniFit overall score based on a sample of 1,282,242 unique test-takers. The Chemofog assessment tests are extracted from this battery. Image subject to Cognifit Creative Commons.

The cutoff point to consider cognitive affectation is 250, as it corresponds to >1SD below the mean (see Figure 3 below). CogniFit assessment is registered with the US Food and Drug Administration (FDA Registration Number: 3017544020, UDI-DI: 00860009958104).

Secondary outcomes

Clinical. Hospital Anxiety and Depression Scale (HADS): Assessed emotional distress through 7 anxiety items (HADS-Anxiety) and 7 depression items (HADS-Depression). The range of scores is 0–21 for each subscale, and 0–42 for the overall questionnaire, where higher scores indicate worse clinical symptoms.[82]

Adherence to Refill and Medication Scale (ARMS-e): Medication adherence will be assessed through the Spanish version[83] of ARMS-e, which is a valid and reliable scale for patients with a chronic disease. This instrument consists of 12 questions: 8 are focused on the patient's consistency in taking medication appropriately and 4 on their proper collection. Lower overall scores correspond to better adherence.

European Quality of Life Scale (EQ-5D- 3L): The EQ-5D provides a measure of Health-Related QoL (HRQoL) and is helpful for the evaluation of the cost-utility of health interventions.[84] Lower scores represent worst health status.

Post-traumatic Stress Disorder Checklist (PCL-5): The PCL-5 is widely used in clinical and research settings to screen for post-traumatic symptoms. Higher scores indicate a higher severity of post-traumatic symptoms.[85]

Work role functioning questionnaire (WRFQ): a self-report assessment tool, validated in cancer patients[86] and in Spanish population,[87] that is used to evaluate an

individual's work-related functioning and productivity. It is specifically designed to measure how mental health symptoms and conditions impact an individual's ability to perform in a work environment. Higher scores indicate better work-related functioning. Patients will be first answered if they are professionally active or in a sick leave, and if they are active, the WRFQ will be administered.

Healthcare experience. Health literacy: Will be measured with a visual analogue scale with the following question (translated from Spanish): '*Please indicate your level of satisfaction with the information provided to you by the Catalan Institute of Oncology (ICO) regarding your illness and treatments, where 0 is very dissatisfied with the information received, and 10 is very satisfied with the information received*'.

Intervention satisfaction: Will be measured with a visual analogue scale with the following question (translated from Spanish): '*Rate from 0 to 10 to what extent you are satisfied with the ICOnnecta't Intervention, where 0 is completely dissatisfied and 10 is completely satisfied*'.

App usability: Will be measured with a visual analogue scale with the following question (translated from Spanish): '*Rate from 0 to 10 to what extent you found the application easy to use, where 0 is very difficult to use and 10 is very easy to use*'.

Variables for the cost-utility analysis comprise EQ5D, use of medical care and psychotropic medication, time off work, professional salaries, infrastructure costs. For more details, see our last study protocol.[88]

Statistical analysis

Data will be analyzed using the Statistical Package of Social Sciences (SPSS, IL, Chicago, version 20) and R Software (version 3.1.2).

Primary outcome analysis. The main analysis will be performed for the intention-to-treat population.

An independent Linear Mixed Models with a cluster of patients will be conducted to examine the evolution of the cognitive outcomes between the two intervention groups (digital stepped psychosocial care vs. digital stepped psychosocial care + cognitive module). Time and group will be used as independent variables. The interaction between time and group will be also assessed. More specifically, one model will approach Subjective Cognition (i.e., FACT-Cog, Perceived Cognitive Impairment sub-scale) and another Objective Cognition (Neurocognitive Index). The models will be repeated adjusted by age and education.

Descriptive statistics (mean, standard deviation) for each group before and after the intervention, as well as at follow ups, will be reported together with effect sizes (e.g., Cohen's d). For all outcomes, 95% confidence intervals (CIs) will be calculated based on estimates and SEs.

Secondary outcome analysis. To analyze the impact of the ecosystem, including ICOgnition, on secondary outcomes such as depression and anxiety levels, distress, quality of life, and patients' healthcare experience. Linear Mixed Models will also be used, following the same procedure described above.

Mediation analysis will be used to assess the effect of emotional distress and posttraumatic stress in cognitive functioning, and whether they mediate the relationship between the interventions and cognitive responses.

Other pre-specified outcome analyses. Discrepancy between Objective and Subjective Measures (baseline and after intervention): First, we will standardize the values to ensure that they are on the same scale through a z-score standardization. Intraclass correlation index (ICC) and Bland-Altman Plot will be used to describe the agreement between the standardized objective and subjective cognition scores. Additionally, linear regression will be made to ascertain for which variables could be explaining the expected discrepancies.

Clusters of cognitive impairment: Hierarchical cluster analysis will be run using cognitive performance data to identify distinct groups of participants with similar cognitive profiles. We will also examine whether the clusters differ in demographic and clinically relevant variables (i.e., cancer treatments) and the intervention response.

Cognitive assessment optimization: The equivalence of online cognitive testing with paper and pencil tests in detecting objective cognitive impairment will be tested.[89–92] Also, the most sensitive test to detect CRCI will be explored.

Economic evaluation. Cost-utility analysis:

Cost-utility analysis (CUA) is a type of economic evaluation used in healthcare to assess the cost-effectiveness of interventions. The primary outcome measure of CUA is cost per quality-adjusted-life-years (QALYs) gained, which allows to compare the cost-effectiveness of different interventions.[93]

A societal perspective for both ICOnnecta't and ICOgnition interventions will be adopted. This perspective will consider direct medical costs (intervention costs, including implementation costs and maintenance costs of the mobile apps; psychotropic medication costs; visits to healthcare professionals for psychosocial or cognitive-related needs) and non-medical costs (costs associated with transportation to the healthcare center for assessments, as fuel expenses or public transportation fares), as well as indirect costs (productivity losses of the study participants like sickness leave and absenteeism). Data on the resource use and unit costs for each cost item will be calculated. Resource use will be measured using patient questionnaires

(e.g., on sickness leave) and by extracting data from medical files. The incremental benefits and costs will be calculated by means of the Incremental Cost-Utility Ratio (ICUR). The formula for ICUR is (CostB - CostA) / (QALY B – QALY A), where CostB and QALY B represent the cost and effect of the new intervention (ICOgnition), and CostA and QALY A represent the cost and effect of the comparator intervention (ICOnnecta't). The uncertainty surrounding the ICUR will be assessed using bootstrapping and projected on a cost-utility plane. A sensitivity analysis will be performed to assess the robustness of our results to explore how uncertainties in various parameters, such as cost estimates and outcome measurements, may impact the findings.

Discussion

The ICOgnition intervention presents a comprehensive and promising preventive approach to address early cognitive difficulties and buffer cognitive impact in newly BC diagnosed patients. The implementation of this intervention holds significant implications for BC patients and potentially for individuals with similar cognitive impairments in other medical conditions.

First of all, identifying the most sensitive cognitive measures for detecting cognitive impairment in breast cancer patients holds significant clinical implications, particularly in reducing the burden on patients who are already navigating numerous medical visits and tests. By pinpointing the most sensitive measures, clinicians can streamline the cognitive assessment process, potentially avoiding the need for administering a long neuropsychological battery. This not only alleviates the burden on cancer patients but also optimizes the utilization of healthcare resources, allowing for more efficient allocation of time and personnel. Also, the use of sensitive cognitive measures allows for more precise monitoring of cognitive changes, which have shown to evolve and change over time.[40] Moreover, it can inform the development of standardized assessment protocols for routine clinical practice allowing healthcare providers consistency in evaluating cognitive function across different clinical settings.

Once the deficits have been efficiently detected, the intervention itself has to be tested. The ICOgnition intervention, designed in steps, holds promise enhancing cognitive function and overall QoL for breast cancer patients. This approach emphasizes early delivering of digital psychosocial support, psychoeducational resources, and personalized cognitive training with proved efficacy[58,94] tailored to each patient's needs. Screening for subjective and objective cognition allows for targeted interventions, including support from health psychologists for emotional distress and flexible access to cognitive modules blocks based on individual needs. Ongoing monthly assessment and transition to cognitive training further ensure personalized intervention delivery, as the timing of intervention initiation is contingent upon the manifestation of cognitive deficits rather than being uniformly applied to all users.

By integrating these elements into digital technology, it will help patients regain cognitive abilities affected by cancer and treatments. Improved cognitive function may lessen distress and anxiety, aiding in adjustment post-diagnosis. Additionally, the intervention may assist in managing daily tasks, sustaining employment and participating in meaningful social interactions.

The ICOgnition intervention may benefit more than just newly diagnosed breast cancer patients. Those at different stages of their cancer journey, or with other types of cancer, as well as individuals with cognitive challenges due to neurological disorders, chronic illnesses or certain medications, could also find value in a similar approach. The tailored combination of psychosocial support, cognitive health literacy, cognitive training and digital interventions could be adapted and tailored to meet the specific needs of patients in various medical settings in a personalized medicine approach. Thus, as cognitive difficulties are common in a range of health conditions, the successful implementation of ICOgnition could provide a template for innovative interventions in other patient populations.

While the protocol for the ICOgnition intervention exhibits promise, it warrants several considerations. First, the complexities inherent in implementing such an intervention demand careful attention, particularly regarding resource allocation and patient adherence, to ascertain its efficacy in real-world settings. Second, conducting an economic evaluation is imperative to gauge the cost-utility and sustainability of the intervention. Third, the study will include recently diagnosed breast cancer patients regardless of the oncological treatments prescribed. Future research should aim to stratify participants based on treatment type and duration to better understand the differential effects of various treatment regimens on cognitive function. In any case, to address potential differences depending on cancer treatments, we have planned to conduct cluster analysis, which will allow us to explore patterns and groupings within our dataset based on treatment regimens. Fourth, as a longitudinal study, we will experience missing data and attrition over time, which may introduce bias and limit the interpretability of our results. We will employ retention strategies such as phone contact reminders to minimize missing data and attrition bias.

Conclusion

The ICOgnition intervention could enhance cognitive function and quality of life for breast cancer patients in early illness stages. It may also offer a useful framework for tackling cognitive challenges in other patient groups. The successful implementation of this intervention could signify a major advancement in holistic patient care. It would

foster a deeper understanding of cognitive impairment in medical settings and drive the development of supportive interventions aimed at improving patients' overall well-being and functional outcomes.

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Data availability: Data available on request due to privacy/ethical restrictions. The data that support the findings of this study are available on request from the corresponding author [MSB].

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