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PSYCARTKIDS: BIO-PSYCHOLOGICAL IMPACT OF COGNITIVE TRAINING AND MINDFULNESS IN CHILDREN AFTER CAR-T THERAPY, HEMATOPOIETIC TRANSPLANTATION, OR CHEMOTHERAPY: MIXED METHODS STUDY AND RANDOMIZED CONTROLLED TRIAL.

BACKGROUND

This project has the objective of implement a randomized controlled clinical trial focused on telematic interventions for cognitive training and mindfulness-based emotional regulation, ending with a follow-up 6 months after treatment.

Hematological and oncological diseases have a clinically significant impact on the mental health, biopsychological functioning, and neurodevelopment of the child and adolescent population affected by them. This assertion is especially applicable to children and adolescents who must undergo intensive therapies, such as high-dose chemotherapy or hematopoietic transplantation (hereinafter HPT); although survival rates have increased significantly, this has been achieved at the cost of greater morbidity in this clinical population (Di Giuseppe et al., 2020). In particular, children and adolescents with acute lymphoblastic leukemia treated with chemotherapy or who subsequently received a HST suffer from a wide range of neurocognitive deficits, although the evidence accumulated to date is inconclusive due to a lack of sufficient studies on the subject. In turn, at the bio-psychological level, patients diagnosed with acute lymphoblastic leukemia experience clinically significant levels of pain (Thompson et al., 2021), as well as high-risk psychological problems (suicidal ideation), which are exacerbated by the increased presence of somatic symptoms (pain, nausea, fatigue, and sleep problems) (Raghubar et al., 2022). This covariation between deficits in certain neurocognitive domains (executive functions) and patterns of somatic symptoms (e.g., chronic pain) increases the degree of disability in children and adolescents by negatively impacting their self-care and adaptive behaviors (Caes et al., 2021).

Fortunately, new therapies are being researched and implemented in subgroups of patients whose diseases evolve with a relapsing clinical course or are resistant to the prescribed treatment. Specifically, chimeric antigen receptor T-cell (CAR-T) therapy is available and has been approved for use in children and adolescents with refractory or relapsed B-cell acute lymphoblastic leukemia (following a relapse after TPH, or after a second relapse). (Ragoonanan et al., 2022). Although scientific research to date provides data on its efficacy and effectiveness, very little research is available on its impact on mental health and neurocognition. This is despite its neurotoxic effects already described in the scientific literature (Ragoonanan et al., 2022), even though this cell therapy is generally safe at the neurological level (Ursu et al., 2022). In this regard, the only two scientific studies that have empirically addressed the potential cognitive impact of this therapy have been conducted exclusively in adult populations diagnosed with lymphoma and using self-reported measurement instruments. concluding that approximately 40% of patients report cognitive complaints, which persist for 1-5 years after CAR-T cell infusion and directly impact their quality of life, both physically and mentally (Kamal et al., 2021).

However, its neurocognitive and psychological impact during critical or sensitive periods of neurodevelopment (i.e., childhood and adolescence); in other diseases such as lymphoblastic leukemia; and in comparison with other cell therapies (hematopoietic transplantation) has not yet been empirically examined. This subject of study is clinically relevant because children and adolescents face different stressors in relation to this new cell therapy, namely: the hematological-oncological disease they suffer from; uncertainty about receiving a novel and relatively recent medical treatment; and the specific neurotoxicity associated with these immunotherapies (whether subacute, due to delayed adverse events, the potential development of cytokine release syndrome, or immune effector cell-associated neurotoxicity syndrome [ICANS]) (Taylor et al., 2022). Therefore, prospective monitoring of

the neurocognitive functioning of patients receiving CAR-T cell therapies must be systematically and imperatively protocolized in routine clinical practice with this clinical population (Shalabi et al., 2021). This will also enable us to optimize its implementation and enhance the durability and consolidation of disease remission following administration of this new cell therapy, thereby stratifying subgroups of patients at higher potential risk of relapse (Shalabi et al.).

Given that research into these new therapies has so far focused exclusively on the adult population, the scientific literature in this area of knowledge advocates a scientific-clinical approach characterized by a neurodevelopmental perspective, adapted to each stage of the patient's life cycle (Taylor et al., 2021). To this end, this research project proposes the following study:

Given the potential complications and neuropsychological sequelae reported after exposure to such medical treatments, there is a striking scientific gap in relation to neurocognitive and psychological interventions for this population of children and adolescents with acute lymphoblastic leukemia exposed to different cell therapies, which is why this project pursue a randomized controlled clinical trial. However, unimodal interventions have proven to be very limited in terms of their transfer to other domains not directly trained (Slattery et al., 2022), which is why this project includes several intervention modalities (cognitive training and mindfulness-based emotional regulation training) whose independent efficacy has only been partially tested in this clinical population, given the very few clinical trials conducted in this regard (Vekety et al., 2021). Specifically, with regard to cognitive training interventions, the only two randomized clinical trials implemented to date in children with acute lymphoblastic leukemia demonstrated efficacy in some neuropsychological domains (working memory and processing speed), with these results being maintained at the 6-month follow-up (Conklin et al., 2017). In turn, mindfulness-based interventions have been shown to be effective, through randomized controlled clinical trials, in improving quality of life and mental health in adult hematopoietic stem cell transplant recipients (Duong et al., 2017). However, these mindfulness-based interventions have not been tested in children and adolescents receiving hematopoietic transplantation or CAR-T therapy, despite being recommended in recent clinical practice guidelines for patients in this age group. (Pathrose et al., 2021). In addition to the gold standard measures for assessing the effectiveness of a non-pharmacological clinical trial (neurocognitive and biopsychological), the scientific literature emphasizes the prognostic and predictive value of incorporating biomarkers (Bai et al., 2022), as well as neurofunctional indicators (connectome), in order to identify new patterns of potential change, whether at the biochemical or neural connectivity level, following the implementation of cognitive training and mindfulness (Kennedy et al., 2022).

In short, there is a significant scientific gap regarding the neurocognitive and biopsychological impact of these CAR-T cell therapies in children and adolescents, as well as the efficacy and effectiveness of non-pharmacological interventions in these patients (Schagen et al., 2022); this is a subject that has not been studied to date by any other national or international research team. In turn, this project is part of an ongoing line of research, which began in April 2021, in children and adolescents who have undergone some type of transplant (solid organ or hematopoietic progenitor), with two projects funded to date, where the PI is the one presenting this new project; it also ties in with another project on neurocognitive training in childhood cancer survivors (PI: Dr. Antonio Pérez Martínez). These two projects in transplanted populations also involve the participation of patients and their families in the form of focus groups, in order to inform future interventions and healthcare protocols. To date, preliminary results from these two related projects show that children and adolescents

exposed to transplantation have clinically relevant problems, both at the neurocognitive level (in terms of intellectual ability, processing speed, attention, memory, visuoconstructive ability, and various executive functions) and mental health (both internalizing and externalizing psychological disorders, as well as the intensity and interference of the pain experienced). These difficulties and deficits have gone unnoticed by their healthcare professionals, who have been treating them for years, and explain part of the resistance to adhering to prescribed treatments and clinical recommendations.

For all the above reasons, this project will contribute to creating a pioneering line of research in this clinical population, both nationally and internationally, establishing itself as a new strategic scientific-translational line that guarantees a humanized and comprehensive healthcare approach, of a biopsychosocial nature, for these patients at a stage of great vulnerability in their neurodevelopment (Steineck et al., 2020; Taylor et al., 2022).

REFERENCES

Bai, J., Withycombe, J., & Eldridge, R. C. (2022). Metabolic Pathways Associated With Psychoneurological Symptoms in Children With Cancer Receiving Chemotherapy. *Biological Research for Nursing*, *24*(3), 281–293. https://doi.org/10.1177/10998004211069619

Boutron, I., Altman, D. G., Moher, D., Schulz, K. F., Ravaud, P., & CONSORT NPT Group. (2017). CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. *Annals of Internal Medicine*, *167*(1), 40–47. https://doi.org/10.7326/M17-0046

Caes, L., Dick, B., Duncan, C., & Allan, J. (2021). The cyclical relation between chronic pain, executive functioning, emotional regulation, and self-management. *Journal of Pediatric Psychology*, *46*(3), 286–292.

Clarke, V., & Braun, V. (2021). *Thematic analysis: A practical guide*. SAGE.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences*. Lawrence Erlbaum Associates.

Cohen, J. (1992). A power primer. *Psychological Bulletin*, *112*(1), 155–159.

Conklin, H. M., Ashford, J. M., Clark, K. N., Martin-Elbahesh, K., Hardy, K. K., Merchant, T. E., Ogg, R. J., Jeha, S., Huang, L., & Zhang, H. (2017). Long-Term Efficacy of Computerized Cognitive Training Among Survivors of Childhood Cancer: A Single-Blind Randomized Controlled Trial. *Journal of Pediatric Psychology*, *42*(2), 220–231. https://doi.org/10.1093/jpepsy/jsw057

Cusatis, R., Balza, J., Uttke, Z., Kode, V., Suelzer, E., Shaw, B. E., & Flynn, K. E. (2023). Patient-reported cognitive function among hematopoietic stem cell transplant and cellular therapy patients: A scoping review. *Quality of Life Research*, *32*(4), 939–964. https://doi.org/10.1007/s11136-022-03258-0

Di Giuseppe, G., Thacker, N., Schechter, T., & Pole, J. D. (2020). Anxiety, depression, and mental health-related quality of life in survivors of pediatric allogeneic hematopoietic stem cell transplantation: A systematic review. *Bone Marrow Transplantation*, *55*(7), 1240–1254. https://doi.org/10.1038/s41409-020-0782-z

Dreneva, A. A., & Devyaterikova, A. A. (2022). Comparative Analysis of Cognitive, Motor, and Visual-Motor Functions in Pediatric Acute Lymphoblastic Leukemia Survivors With and Without Allogeneic Hematopoietic Stem Cell Transplantation. *Archives of Clinical Neuropsychology: The Official Journal of the National Academy of Neuropsychologists*, *37*(7), 1493–1501. https://doi.org/10.1093/arclin/acac038

Duong, N., Davis, H., Robinson, P. D., Oberoi, S., Cataudella, D., Culos-Reed, S. N., Gibson, F., Götte, M., Hinds, P., Nijhof, S. L., Tomlinson, D., van der Torre, P., Ladas, E., Cabral, S., Dupuis, L. L., & Sung, L. (2017). Mind and body practices for fatigue reduction in patients with cancer and hematopoietic stem cell transplant recipients: A systematic review and meta-analysis. *Critical Reviews in Oncology/Hematology*, *120*, 210–216. https://doi.org/10.1016/j.critrevonc.2017.11.011

Fontes-de-Gracia, S., García-Gallego, C., Quintanilla-Cobián, L., Rodríguez-Fernández, R., & Sarriá-Sánchez, E. (2020). *Fundamentos de investigación en Psicología*. Editorial UNED.

Kamal, M., Joseph, J., Greenbaum, U., Hicklen, R., Kebriaei, P., Srour, S. A., & Wang, X. S. (2021). Patient-Reported Outcomes for Cancer Patients with Hematological Malignancies Undergoing Chimeric Antigen Receptor T Cell Therapy: A Systematic Review. *Transplantation and Cellular Therapy*, *27*(5), 390.e1-390.e7. https://doi.org/10.1016/j.jtct.2021.01.003

Kennedy, M., Mohamed, A. Z., Schwenn, P., Beaudequin, D., Shan, Z., Hermens, D. F., & Lagopoulos, J. (2022). The effect of mindfulness training on resting-state networks in pre-

adolescent children with sub-clinical anxiety related attention impairments. *Brain Imaging and Behavior*, *16*(4), 1902–1913. https://doi.org/10.1007/s11682-022-00673-2

Medina, R., Bouhaben, J., de Ramón, I., Cuesta, P., Antón-Toro, L., Pacios, J., Quintero, J., Ramos-Quiroga, J. A., & Maestú, F. (2021). Electrophysiological Brain Changes Associated With Cognitive Improvement in a Pediatric Attention Deficit Hyperactivity Disorder Digital Artificial Intelligence-Driven Intervention: Randomized Controlled Trial. *Journal of Medical Internet Research*, *23*(11), e25466. https://doi.org/10.2196/25466

Pathrose, S., Everett, B., Patterson, P., Ussher, J., Salamonson, Y., McDonald, F., Biegel, G., & Ramjan, L. (2021). Mindfulness-Based Interventions for Young People With Cancer: An Integrative Literature Review. *Cancer Nursing*, *44*(5). https://doi.org/10.1097/NCC.0000000000000821

Podsakoff, P. M., MacKenzie, S. B., & Podsakoff, N. P. (2012). Sources of method bias in social science research and recommendations on how to control it. *Annual Review of Psychology*, *63*, 539–569. https://doi.org/10.1146/annurev-psych-120710-100452

Raghubar, K. P., Chambers, T., Hill, R. M., Taylor, O., Hockenberry, M., Hooke, M. C., Mitby, P., Moore, I. K., Brown, A. L., & Scheurer, M. E. (2022). Longitudinal investigation of suicidal ideation and associated factors during pediatric acute lymphoblastic leukemia chemotherapy. *Psycho-Oncology*, *31*(10), 1782–1789. https://doi.org/10.1002/pon.6014

Ragoonanan, D., Sheikh, I. N., Gupta, S., Khazal, S. J., Tewari, P., Petropoulos, D., Li, S., & Mahadeo, K. M. (2022). The Evolution of Chimeric Antigen Receptor T-Cell Therapy in Children, Adolescents and Young Adults with Acute Lymphoblastic Leukemia. *Biomedicines*, *10*(9), 2286. https://doi.org/10.3390/biomedicines10092286

Schagen, S. B., Tsvetkov, A. S., Compter, A., & Wefel, J. S. (2022). Cognitive adverse effects of chemotherapy and immunotherapy: Are interventions within reach? *Nature Reviews. Neurology*, *18*(3), 173–185. https://doi.org/10.1038/s41582-021-00617-2

Shalabi, H., Gust, J., Taraseviciute, A., Wolters, P. L., Leahy, A. B., Sandi, C., Laetsch, T. W., Wiener, L., Gardner, R. A., Nussenblatt, V., Hill, J. A., Curran, K. J., Olson, T. S., Annesley, C., Wang, H.-W., Khan, J., Pasquini, M. C., Duncan, C. N., Grupp, S. A., … Shah, N. N. (2021). Beyond the storm—Subacute toxicities and late effects in children receiving CAR T cells. *Nature Reviews. Clinical Oncology*, *18*(6), 363–378. https://doi.org/10.1038/s41571-020-00456-y

Slattery, E. J., O'Callaghan, E., Ryan, P., Fortune, D. G., & McAvinue, L. P. (2022). Popular interventions to enhance sustained attention in children and adolescents: A critical systematic review. *Neuroscience and Biobehavioral Reviews*, *137*, 104633. https://doi.org/10.1016/j.neubiorev.2022.104633

Steineck, A., Wiener, L., Mack, J. W., Shah, N. N., Summers, C., & Rosenberg, A. R. (2020). Psychosocial care for children receiving chimeric antigen receptor (CAR) T-cell therapy. *Pediatric Blood & Cancer*, *67*(5), e28249. https://doi.org/10.1002/pbc.28249

Taylor, M. R., Knight, J. M., & Rosenberg, A. R. (2021). The biology of stress in cancer: Applying the biobehavioral framework to adolescent and young adult oncology research. *Brain, Behavior, & Immunity - Health*, *17*, 100321. https://doi.org/10.1016/j.bbih.2021.100321

Taylor, M. R., Steineck, A., Lahijani, S., Hall, A. G., Jim, H. S. L., Phelan, R., & Knight, J. M. (2022). Biobehavioral Implications of Chimeric Antigen Receptor T-cell Therapy: Current State and Future Directions. *Transplantation and Cellular Therapy*, S2666-6367(22)01668-2. https://doi.org/10.1016/j.jtct.2022.09.029

Thompson, J., Fisher, B., Sung, L., Dvorak, C., Dang, H., Lo, T., & Alexander, S. (2021). Musculoskeletal impairments in children receiving intensive therapy for acute leukemia or undergoing hematopoietic stem cell transplant: A report from the Children's Oncology Group. *Pediatric Blood & Cancer*, *68*(8), e29053. https://doi.org/10.1002/pbc.29053

Tong, A., Sainsbury, P., & Craig, J. (2007). Consolidated criteria for reporting qualitative research (COREQ): A 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care: Journal of the International Society for Quality in Health Care*, *19*(6), 349–357. https://doi.org/10.1093/intqhc/mzm042

Ursu, R., Maillet, D., Belin, C., Moroni, C., Cuzzubbo, S., Vernier, V., Sirven-Villaros, L., Carreau, C., Di Blasi, R., Thieblemont, C., & Carpentier, A. F. (2022). Long-term Neurologic Safety in Patients With B-Cell Lymphoma Treated With Anti-CD19 Chimeric Antigen Receptor T-Cell Therapy. *Neurology*, *99*(12), 511–515. https://doi.org/10.1212/WNL.0000000000201083

Vekety, B., Logemann, H. A., & Takacs, Z. K. (2021). The effect of mindfulness-based interventions on inattentive and hyperactive–impulsive behavior in childhood: A meta-analysis. *International Journal of Behavioral Development*, *45*(2), 133–145.

HYPOTHESES

The following are the hypotheses predicted for the study:

1. Statistically significant changes will be observed at the neurocognitive, biopsychological, and connectome levels after multimodal treatment (cognitive training and mindfulness) compared to the waiting list group.
2. Statistically significant changes will be observed at the neurocognitive, biopsychological, and connectome levels between the two intervention sequences: 1st cognitive training and 2nd mindfulness versus 1st mindfulness and 2nd cognitive training.

OBJECTIVES

1. To analyze the efficacy of multimodal treatment (cognitive training and mindfulness-based emotional regulation intervention) compared to a control group on neurocognitive, biopsychological, biomarker, and connectome outcome variables.
2. Compare the effectiveness of the two intervention sequences (1st cognitive training and 2nd mindfulness versus 1st mindfulness and 2nd cognitive training) on neurocognitive, biopsychological, biomarker, and connectome outcome variables.

METHODS

1. Study Design 3: In this single-center study (La Paz University Hospital), the pilot phase of a randomized, counterbalanced, crossover controlled clinical trial with a recycled waiting list will be conducted according to CONSORT standards. (Boutron et al., 2017).

2. Participants: A total of 40 patients (20 patients initially in the clinical trial phase and 20 on the waiting list) between the ages of 8 and 18 will be recruited from the three clinical groups in Study 1, requiring compliance with inclusion criteria (having a computer, mobile phone, or tablet with an Internet connection) and exclusion criteria (CI < 80 in Matrices). These 40 patients will be recruited from the sample participating in Study 1 using a strategic/intentional non-random sampling technique.

3. Outcome variables: In pre-/post-intervention phases, primary variables will be measured using performance tests: processing speed (SDMT); sustained visual attention (CPT-3); working memory, implicit, immediate/delayed auditory-verbal, visual-spatial, and intermodal [Clinical Memory Assessment (ECM)]; verbal fluency [Verbal Fluency Test (VFT)]; resistance to visual interference [Colors and Words Test (STROOP)]. Secondary variables in pre-/post-intervention phases are questionnaires measuring: executive functions [BRIEF-2, parent-completed version]; pain intensity and interference [BPI, self-reported by patient]; sleep quality [PROMIS and AIQ, self-reported by patient]; emotional and behavioral problems [BASC-3, parent and self-reported versions]; and mindfulness, trait level [Children and Adolescent Mindfulness Measure (CAMM)]; as well as biomarkers (inflammatory and immunological) and a neurofunctional analysis (connectome), using electroencephalogram (EEG) recordings. In the intermediate phase (3 months after the start of treatment), the BASC-3 questionnaire will be administered. Finally, at the 6-month follow-up after the end of both interventions, the BRIEF-2, BASC-3, BPI, AIQ, and PROMIS questionnaires will be included.

4. Procedure: Participants will be randomized into two subgroups, which will be equally randomized into one of the following two intervention implementation sequences, according to an intragroup Latin square equal weighting technique (AB/BA design). (Fontes-de-Gracia et al., 2020): 1st sequence) Cognitive training (weeks 1-12) + Mindfulness-based emotional regulation (weeks 13-24); 2nd sequence) Mindfulness-based emotional regulation (weeks 1-12) + Cognitive training (weeks 13-24). This equal weighting technique will allow for systematic control of progressive error (order or period), without the need for a washout period between the two interventions, due to a potential residual or carry-over effect, as the treatments do not interfere with each other and are of a different nature (neurocognitive intervention versus emotional intervention).

Each intervention will last 12 weekly sessions, with a total sequence of 24 weeks for both treatments. The group of participants on the waiting list (control group) will remain there until after the 24 sessions, at which point they will begin the same process described above for randomization into subgroups and sequences for implementation of the interventions. Each treatment sequence will have a total of 10 participants assigned to it, in two age-differentiated groups (8-12 versus 13-18 years old), with 5 participants per group. Given this small sample size per group, in order to facilitate smooth interaction among participants, one of the pre-intervention scores (Emotional Regulation Index, BRIEF-2) will be used as a blocking variable, in addition to age, artificially dichotomized according to a cutoff point (resulting in low and high values on that index), thus maximizing the control of extraneous intergroup variables. Consequently, four subgroups of patients will be created by combining the levels of two blocking variables: age (8-12 versus 13-18 years) and Emotional Regulation Index score (low versus high values).

Subsequently, after assigning an anonymized code to each patient, using web-based randomization software, each treatment administration sequence (AB/BA) will be randomly assigned to each of the four patient subgroups.

On the one hand, the cognitive training intervention will use the Sincrolab platform, which guarantees security and confidentiality and has been validated in clinical populations of children and adolescents (Medina et al., 2021). Four weekly sessions of 15 minutes each will be prescribed, training neurocognitive functions such as attention, memory, visuospatial skills, and executive functions. This platform provides regular reports on the use and fulfillment of objectives for each participant. In addition, once a week, online and also in the afternoon for 60 minutes, a group video call will be held with all participants to discuss difficulties and obstacles in using the platform, as well as to promote full adherence to the weekly usage guidelines. All these sessions will be moderated by the principal investigator of this project. In the event of less than 50% weekly adherence to the use of Sincrolab, the research team will make a weekly call to the participant and their legal guardians to encourage greater compliance. On the other hand, mindfulness-based emotional regulation interventions will be carried out in groups and online (video calls), following intervention protocols that have already been validated in children and adolescents in this online format (Pathrose et al., 2021). Each weekly session will last 60 minutes, with practice tasks prescribed for everyday contexts (four weekly tasks of 15 minutes each). To this end, a web repository will be used, with two versions differentiated by age range (children versus adolescents), from which material (comics and audio files for practicing mindfulness-based exercises) will be extracted to put emotional regulation skills into practice independently at home. The two interventions in each treatment sequence have the same duration and weekly workload for independent work. Each intervention implementation sequence will be preceded by a pre-intervention assessment, followed by an intermediate assessment before the change in treatment administration sequence, and ending with a post-intervention assessment (the same as the pre-intervention assessment). The connectome will be measured both at rest and during an activity (the neurocognitive assessment tests themselves) carried out by technical staff from an external company. Both the neurocognitive assessment and the connectome assessment will be carried out individually and in person at the hospital facilities, one month before the start of each treatment sequence. Biomarkers will be extracted from routine control tests. Finally, the questionnaires (for patients and their legal guardians) will be completed via electronic links from the publishers that market them (BRIEF-2 and BASC-3), as well as REDCap (BPI, PROMIS, AIQ, and CAMM).

5. Statistical analyses: The statistical analyses for this third study will be described jointly for the two established objectives.

First, mixed 2x3 ANCOVAs will be used (intergroup factor, with two levels: experimental group versus control; and repeated measures factor, with three levels: pre-intervention, post-intervention, and six months), controlling for confounding variables (time elapsed since completion of the last treatment received: chemotherapy, TPH, or CAR-T). However, in the event of non-compliance with statistical assumptions such as normality, non-parametric analog models will be used. In turn, latent growth curve models will be developed.

As for the intergroup factor, Tukey's HSD parametric tests (for homoscedastic contrasts) and Games-Howell tests (for heteroscedastic contrasts) will be used to control the type I error rate per family of comparisons. Likewise, in the event of non-compliance with parametric assumptions such as normality, the Mann-Whitney U test will be used for pairwise comparisons, controlling the type I error rate with the Bonferroni correction. Regarding the intragroup factor, parametric pairwise contrasts will be performed using Tukey's WSD test (for spherical contrasts) and the

Roy-Bose test (for non-spherical contrasts); and non-parametric pairwise comparisons will be performed using the Wilcoxon test together with a Dunn-Sidak post hoc correction.

In turn, these parametric hypothesis testing procedures will be complemented with effect size indices such as omega squared, as an omnibus index, and Cohen's d, as an index for pairwise comparisons.

Conversely, where appropriate, for the intergroup factor, effect size indices for nonparametric tests such as Freeman's Theta, as an omnibus index, and Cliff's Delta, as an index for pairwise comparisons, will be used. On the other hand, for the intragroup factor, Kendall's W-type omnibus effect size indices will be applied, as well as the biserial correlation for dependent pair ranks in order to perform multiple comparisons.

Finally, for the interactive term, the effect size index f will be chosen as an omnibus test, and Cohen's d indices for simple effects.

Finally, multiple regression analyses will be performed to predict post-treatment and 6-month follow-up measures (neurocognitive and biopsychological), coding some measures from Study 1 as predictors, such as: processing speed levels, sustained visual attention, verbal fluency, and resistance to visual interference.

6. Limitations, biases, and contingency plan: given that participant loss is expected in any clinical trial, additional participants from the previous study will be recruited in such a scenario. The multi-method evaluation approach used (objective neurocognitive tests, questionnaires, biomarkers, and connectome) will avoid the common method bias (Podsakoff et al., 2012). Anticipating the temporary limitation on pre-/post-intervention assessment tasks as a potential risk to implementation, the age-differentiated treatment editions will be implemented partially simultaneously, with a one-month delay in the start of the intervention for each age group, using that month for the pre-intervention assessment of the other group.

This project will be carried out in accordance with the ethical principles of the Fortaleza Declaration of Helsinki (2013), strictly respecting confidentiality and the requirements of Spanish/European data protection regulations, as well as the provisions of the biomedical research law (Law 14/2007, of July 3); the informed consent of patients and their legal guardians will be required.

Finally, given that the objectives of these studies have not been scientifically addressed to date in the child and adolescent population receiving CAR-T therapies, this project will make a novel, original, and relevant contribution at the scientific-clinical level, and is in line with one of the strategic lines of our institution, IdiPAZ, and its core hospital, given that it coordinates the **European Reference Network TransplantChild.**

DATA MANAGEMENT PLAN

The data management plan will include criteria for the handling and administration of scientific data following the FAIR principles (Findable, Accessible, Interoperable, and Reusable).

TYPE OF DATA: The data obtained from study participants are clinical (neurocognitive and biopsychological) and laboratory parameters, excluding genetic data. These data may be collected directly from individuals who agree to participate in the project, through clinical and/or laboratory tests. Likewise, in some circumstances, existing data in their medical records may be used and accessed by healthcare personnel with the consent of each participant. All of the above information will be included in greater detail in the Data Management Plan that will be developed for the project before its start and prior to the collection of personal data. Patients will be assigned a unique identifier and will be stored anonymously.

ACCESS PROCEDURE: The variables to be studied will be stored in a digital data collection notebook (REDCap), which will serve as a database protected by an authentication system using a user code and password, to which only project researchers will have access. This database will be hosted on the servers of La Paz University Hospital, which complies with security regulations in this area, adopting the appropriate security measures in terms of access and storage. No copies will be stored on personal computers.

OWNERSHIP: Ownership of the personal data to be processed during the course of the project will belong to each of the patients who have provided such data, who will sign an informed consent form to participate in the project. The data controller will be La Paz University Hospital (HULP). The informed consent form will reflect this information, as well as the data to be processed, the purpose for which it is collected, the medium on which it will be stored, the storage period, and the measures that will be implemented to maintain its security. The informed consent form will be drawn up in accordance with current regulations regarding the guarantee of participants' rights.

RESPONSIBILITIES AND ROLES: The PI will be responsible for supervising the data generated by the group during the project and the data management plan.

REPOSITORY: The data used, both intermediate and final, will be uploaded to the most appropriate repositories according to their type. A suitable repository is considered to be a Trusted Digital Repository (TDR), understood as one whose mission is to "provide reliable long-term access to managed digital resources to a designated community, now and in the future" (Research Libraries Group, 2002). The chosen repository must follow the OASIS reference model, developed by the Consultative Committee for Space Data Systems, whose purpose is to generate a standard for the long-term preservation of data that could be used by any organization, regardless of the nature of the information to be preserved. The current version of this model is covered by ISO 14721:2012. Thus, these data, as well as the publications derived from the development of the project, will be published, among others, in the Institutional REPository of SALUD of the Carlos III Health Institute (REPISALUD, https://repisalud.isciii.es/), and in the Institutional Repository of the Regional Ministry of Health of the Community of Madrid (https://repositoriosaludmadrid.es).

Access for other researchers who may be legitimately interested will in any case be subject to approval, complying with the requirement of open access in a restricted environment in accordance with the nature of personal data.

SPECIFIC ETHICAL OR LEGAL REQUIREMENTS APPLICABLE: The data used for the development of this project will be processed in accordance with the provisions of current legislation: Organic Law 3/2018 on the Protection of Personal Data and Guarantee of Digital Rights and Regulation (EU) 2016/679 of the European Parliament and of the Council on the protection of natural persons with regard to the processing of personal data and on the free movement of such data. It will also obtain the favorable opinion of a research ethics committee. The provisions of Law 14/2007, of July 3, on Biomedical Research, will also apply.

INTELLECTUAL PROPERTY: The results of the project that may lead to new diagnostic techniques, modifications to existing treatments and/or protocols, medicines, medical devices, or vaccines will initially be communicated confidentially to the institution by the PI in order to determine whether they could be patentable or should be protected by intellectual property rights. The data may not be disclosed until the patents related to the research are protected, if any, or the appropriate measures are taken to protect the intangible assets.

WORK PLAN

The research team formally involved in this project consists of:
-Psychologists trained in neuropsychology to perform neurocognitive and biopsychological assessments and interpret their data: Eduardo Fernández Jiménez (EFJ) and Cristina Campoy Lacasa (CCL)
-Hematologists/oncologists to refer participants to the project, record biomarkers, and medically interpret the results: Víctor Galán Gómez (VGG), David Bueno Sánchez (DBS), Víctor Quintero Calcaño (VMQC), Mª Isabel Benítez Carabante (MIBC), and María Trabazo del Castillo (MTdC).
-Teaching and research staff: Mª Fe Bravo Ortiz (MFBO), expert in psychotherapeutic interventions; Rocío de la Vega de Carranza (RdlVdC), national reference for pain in children and adolescents and telemedicine; and Alejandro Alberca González (AAG), expert in health technologies.
-Formal collaboration of a representative of the Spanish Association Against Cancer (citizen participation): María Eugenia Bustelo Almeida (MEBA), to identify unmet needs during the care process.
-Additional citizen participation (non-formal collaborators) from ASION: Virginia Martínez García (VMG) and Alicia Moraleda Sánchez (AMS); to identify unmet needs during the care process.

PROJECT DEVELOPMENT STAGES

-**November-December 2025** (experimental group) and **July-August 2026** (recycled waiting list): Pre-intervention neurocognitive, biopsychological (conducted by psychologists), and connectome (conducted by an external company) assessment.
-**March 2026-July 2026** (experimental group) and **September 2026-February 2027** (recycled waiting list): Cognitive training and mindfulness.
-**July-August 2026** (experimental group) and **March-April 2027** (recycled waiting list): Post-intervention neurocognitive, biopsychological, and connectome assessment.
-**December 2026** (experimental group) and **August 2027** (recycled waiting list): Bio-psychological assessment at 6 months follow-up.
-**November-December 2027**: Data extraction, database completion, data analysis, and scientific dissemination (preparation of the fourth article for a JCR specialized journal and conferences).
-**November-December 2027**: Dissemination of results through associations and the media.

IMPLEMENTATION RISKS, CONTROL PLANNING, AND CONTINGENCY PLAN

1) Delay in commencement due to lack of approval from the Ethics Committee: said approval will be processed after publication of the provisional resolution granting this call for proposals.
2) Personnel risks: in the event of a potential drop in the participation of collaborators, a researcher with a similar profile will be added to the team to carry out those tasks.
3) Time risks: the interim monitoring report will assess the degree of project implementation in accordance with the initial planning. In the event of a delay, an extension of the project similar to the length of the delay will be requested, which will not exceed the maximum allowed.
4) Economic-administrative implementation risks: an initial meeting will be held with the institution's public project managers to determine the expenses to be processed in accordance with the Public Sector Contracts Law and to plan their management, with coordination and follow-up meetings being held with these managers. Finally, it is stated that the execution of the project is feasible with the current design and methodology, that the probability of the identified risks is low, and that their impact is moderate. A checklist of potential risks has been designed and these will be monitored every six months, in addition to an interim scientific and execution evaluation (including a risk assessment) and a final evaluation of the project.

AVAILABLE RESOURCES / PROJECT FEASIBILITY

In order to carry out the three studies that make up this project in a feasible and efficient manner, the following resources are already available, as detailed below.

HUMAN RESOURCES

The Child and Adolescent Mental Health Unit, to which the principal investigator of this project is attached, implements therapeutic interventions, either in person or online, with these patients as part of its structural care activity. Therefore, the interventions that make up this study will be feasible as they are incorporated into our usual clinical practice.

In turn, La Paz University Hospital and the two research groups with which the PI of this project collaborates systematically promote the completion of doctoral theses within the framework of projects already in progress, ensuring a constructive learning environment and constant supervision for the effective acquisition of scientific skills by potential doctoral students, as has been done to date with doctoral theses and master's theses under the direction of this PI. Consequently, the active participation of residents in this project who are undergoing their Specialized Health Training in the hospital's Pediatric Hemato-Oncology or Psychiatry, Clinical Psychology, and Mental Health services will be encouraged, so that they can develop their doctoral thesis with the results derived from the project.

MATERIAL RESOURCES

The Child and Adolescent Mental Health Unit at La Paz University Hospital has numerous offices (eight available in the afternoon and three in the morning) equipped with computers with internet connection, telephones, webcams, and microphones to contact participants by phone, carry out thematic interventions, and conduct all face-to-face assessments.