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DECREASE: Decrease Cognitive Decline in Alzheimer's Disease Through Occupational Therapy: A Randomized Controlled Phase III Trial Protocol

Niels Pacheco-Barrios[1], Leandra Ramin-Wright[2]*, Sandra Zhong[3], Cecilia Plaza[4], Aala Elhadi[5], Marion Stokvis[6], Alanna Barrios[7], João Kasakewitch[8], Gloria Rodriguez[9], Stefany Alfaro[10], Guilherme Areas[11], Mariana Batista[12], Lucas Brasil[13], Deborah Estrella[14], Camila García[15], Hana Hastor[16], Renata Medeiros[17], Vítor M. F. Melo[18], Luis Perez[19], Cristina J Ponce[20], Siyer Roohani[21], Nayara Rutes[22], Jose Winter[23], Elsa Yovera[24]

[1] Alberto Hurtado Medical School, Cayetano Heredia Peruvian University, Lima, Peru; [2] University of Basel, Basel, Switzerland; [3] AscenZion Neuromodulation Co., Singapore City, Singapore; [4] Clinica Alemana de Santiago, Chile; [5] Rashid Hospital, Dubai, UAE; [6] Francisco Marroquín University, Guatemala, Guatemala; [7] Tecnologico de Monterrey, School of Medicine and Health Sciences, Monterrey, Nuevo Leon, Mexico; [8] BIDMC, Department of Surgery, Harvard Medical School, Boston, MA, USA; [9] University of Texas, Rio Grande Valley, USA; [10] Universidad Nacional Mayor de San Marcos, Lima, Peru; [11] Physiology Science Department, Universidade Federal do Amazonas, Amazonas, Brazil; [12] Cancer Institute of the State of São Paulo, Brazil; [13] Hospital Alemão Oswaldo Cruz, São Paulo, Brazil; [14] Federal University of Minas Gerais, Brazil; [15] Pontificia Universidad Católica Madre y Maestra, Dominican Republic; [16] Berlin Institute of Health, Charité – Universitätsmedizin, Berlin, Germany; [17] Eurofarma, São Paulo, Brazil; [18] Universidade Salvador, Brazil; [19] Hospital Guillermo Almenara Irigoyen, Lima, Peru; [20] Beth Israel Deaconess Medical Center, Boston, MA, USA; [21] Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt Universität zu Berlin; [22] Hospital Alemão Oswaldo Cruz, São Paulo, Brazil; [23] Facultad de Medicina, Universidad del Desarrollo, Clinica Alemana de Santiago, Chile; [24] National Institute of Health, Lima, Peru.

Abstract

Introduction: *Alzheimer's disease (AD) accounts for more than 80% of dementia cases worldwide and imposes a significant economic burden on the healthcare system. Currently, there is no cure for AD, and pharmacological treatments alleviate AD symptoms but fail to decrease cognitive decline. Occupational Therapy (OT) for AD patients targets symptoms without the side effects of drugs and may even play a disease-modifying role by preserving cognitive functions. The DECREASE trial aims to assess the effectiveness of a cognitive-based OT intervention amongst AD patients.*

Methods: *The DECREASE Trial is a randomized, controlled, multicentric, phase III, superiority trial comparing the effect of OT and standard of care versus standard of care alone on cognition in AD patients. OT will entail a five-week group cognitive rehabilitation program with remote maintenance sessions until six months of follow-up. We will include 278 mild AD patients aged between 65 and 80. Changes in cognitive function between groups will be measured and compared by the ADAS-cog after six months.*

Discussion: *The strengths of this OT program are that it is non-invasive, safe, highly standardized, and accessible to occupational therapists and caretakers worldwide. There is broad evidence of the benefits of functionality. Nevertheless, there needs to be more literature on its effect on cognitive function. AD is a public health emergency that needs to be promptly addressed. This trial will finally determine if an OT-based intervention can decrease cognitive decline and whether it should be included in the standard of care for AD.*

*Corresponding author: leandra.ramin-wright@unibas.ch
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Introduction

Alzheimer's disease (AD) is the most common cause of dementia and accounts for more than 80% of dementia cases worldwide. An estimated 135.46 million patients will be suffering from AD in 2050, which may impose a significant economic burden on the

healthcare system (Alzheimer's Association, 2015; Winblad et al., 2016).

Currently, there is no cure for AD. Pharmacological treatments to manage cognitive decline in AD include cholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists (Rabins et al., 2007). These therapies solely alleviate AD symptoms but fail to modify disease progression in terms of decreasing cognitive decline (Feldman et al., 2007; Qaseem et al., 2008; Raina et al., 2008). Also, pharmacologic treatment is associated with a risk of adverse events (Tricco et al., 2013). Cholinesterase inhibitors can induce vomiting, diarrhea, and arrhythmias (Singh & Sadiq, 2022). NMDA receptor antagonists' adverse effects include dizziness, agitation, or constipation (Olivares et al., 2012). Beyond symptomatic relief, another meaningful therapeutic goal in AD is to delay cognitive decline through new innovative therapies.

Amongst the various treatment measures, Occupational Therapy (OT) stands out as a pragmatic treatment for patients with AD. OT targets symptoms without the side effects of the drugs mentioned above. OT may even play a disease-modifying role in AD by preserving cognitive functions through the repeated practice of everyday tasks where the involvement of cognition is essential for their performance (Ham et al., 2021).

Inclusion of cognitive-focused OT in standard medical treatment may slow the deterioration of cognition in AD, which is superior to symptom relief through drugs, giving this population more time to remain independent and ultimately improving the quality of life for the patient with AD, their families, and societal healthcare burdens.

Among various trials evaluating the use of OT in patients with AD, two trials involving innovative forms of cognitive-focused OT presented initial evidence of improving cognitive function in early-stage AD (Fong et al., 2019; Jo et al., 2018).

In the study by Griffin et al., patients with early-stage AD received OT according to the SMART program, a group cognitive rehabilitation program delivered on an outpatient basis (Griffin et al., 2022). Post-hoc results showed a significant improvement in memory function. In another study by Kim et al. in 2020, an RCT on patients with early-stage AD showed that "Recollection-based OT" significantly improved cognitive functions compared to the standard therapy group (Kim, 2020). The small sample size and short follow-up time are significant limitations of the trial.

Although innovative OT methods such as the SMART program and Recollection-based OT program have shown encouraging results in improving several aspects of AD, such as behavioral symptoms and motor processing, there is still scarce evidence on the impact of decreased cognitive decline on the progression of AD, as measured by the Alzheimer's Disease Cognitive Subscale (ADAS-Cog), and the longer-term effect on cognition of patients with AD beyond three months.

Our primary objective is to evaluate if the addition of cognitive-focused OT, along with standard medical therapy, in comparison to standard medical treatment alone, can decrease cognitive decline as measured by ADAS-Cog in patients with early-stage Alzheimer's Disease aged 65 to 80 years over six months. We hypothesize that cognitive-focused OT with standard medical treatment is better than standard medical treatment alone in decreasing cognitive decline.

Besides our primary objective of decreasing cognitive decline, secondary endpoints are to assess the Reliable Change Index (RCI) of the ADAS-Cog and caregiver burden. Also, the quality of life and functionality of patients with early-stage AD will be assessed at six months of follow-up.

Materials and Methods

The DECREASE trial is designed as a randomized, controlled, multicentric, phase III superiority trial. It is a parallel group design comparing the intervention of OT and standard of care versus standard of care alone. OT will entail the Specialized Memory and Attention Rehabilitation Therapy program (SMART) (Griffin et al., 2022). It comprises a five-week group cognitive rehabilitation program delivered weekly for at least 1.5 hours per session in groups of up to six participants. Group sessions explain dementia, attention, and memory and set goals, strategies, and tasks for patients and family members/caregivers, who are encouraged to participate. Additionally, each participant is also assessed individually by the occupational therapist to identify single memory-related functional goals. Remote maintenance sessions will be carried out from the third to the sixth month of follow-up.

The standard of care includes pharmacological treatment, i.e., NMDA receptor antagonists and cholinesterase inhibitors, according to current American Psychiatric Association (APA) guidelines (Rabins et al., 2007). All patients will continue their standard of care treatment when entering the trial.

Therapy sessions will occur at three hospitals, one at the Alzheimer's Disease Center in Boston and the other at the Tufts Medical Center Neurodegenerative (Dementia) Disorders Program in Boston. The third center will be the Johns Hopkins Memory and Alzheimer's Treatment Center in Baltimore. These health centers are selected because they are dedicated to working with neurodegenerative diseases,

and they provide the certainty that the therapies will be given by doctors with more knowledge of the disease than in a conventional health center.

Participants will be randomly assigned to a control or experimental group with a 1:1 allocation using permuted blocks of four or six random sizes stratified by site. The randomization sequence will be computer generated using STATA®/BE 17.0 (StataCorp LLC, TX, US).

Allocation concealment will be ensured through central randomization, as the allocation sequence performed in STATA®/BE 17.0 will not release the randomization code until the patient has been recruited into the trial, which takes place after affirmative response to informed consent and all baseline measurements have been completed. This makes it impossible for physicians to know which randomization group their patients will be assigned to during recruitment.

This is an open-label study. To reduce bias, blinding will involve outcome assessors and statisticians. Trial participants and care providers won't be masked, as the allocation will be apparent as soon as OT is started. Emergency unblinding will not be necessary in this trial. Clinicians and patients are aware of their allocation. Therefore, if issues evolve with the safety of patients, no unblinding is required. There is no need for statisticians or outcome assessors to be unblinded.

Patients must complete the informed consent and fulfill the inclusion criteria to be eligible for randomization. Inclusion criteria are patients 1) with a diagnosis of Alzheimer's disease with scale stage 3 or 4 of the Functional Assessment Staging Tool for Alzheimer's (FAST) score and Global Deterioration Scale (GDS) level 4 (Alzheimer's Association, 2015; Rabins et al., 2007; Winblad et al., 2016), 2) without more than two years after diagnosis, 3) currently under treatment with Donepezil, Galantamine and/or Rivastgmine, 4) between 65 and 80 years of age. Exclusion criteria comprise patients 1) receiving nonstandard treatments/interventions for mild AD, 2) Acupuncture, hydrotherapy, cognitive behavioral therapy, memantine, 3) with a clinical diagnosis of hypothyroidism, 4) with a clinical diagnosis of current major depressive disorder, 5) with a clinical diagnosis of other forms of dementia (Lewy bodies, vascular, traumatic, frontotemporal), 6) currently under another clinical trial (either for dementia or other diseases), 7) Stages >4 in FAST scale and >3 in GDS or stages <3 in FAST and <4 in GDS., 8) going through hospitalization due to other comorbidities, being unable to complete the OT sessions, and 9) any physical or psychological condition that significantly limits the study participation, including limb amputation. Patients will be recruited through Geriatric/Gerontologic community clinics, academic hospitals (outpatient clinics), and private medical practices that treat patients aged 65 to 80 years diagnosed with mild Alzheimer's Disease and who fulfill the inclusion criteria for the DECREASE trial. The recruitment process will be done by physicians and nurses in charge at each research center.

As a part of the recruitment process, participants or their family members will be helped to fill out the informed consent and a short revision of the inclusion/exclusion criteria. A brief explanation of the DECREASE Trial will be shared with both parties.

Posters will be placed in clinics inviting participants to participate in the trial with contact information should they be interested in participating in the DECREASE trial. Posters will also be placed in Community Centers and Hospital Outpatient Clinics. Physicians will be asked to share mailing lists to invite outpatient participation in the trial. Physicians and nurses will be informed about the DECREASE trial and provided with contact information to refer patients and family members who wish to participate.

Each center will have a leading investigator/physician and a leading nurse investigator previously trained to recruit patients into the study. Also, each center will have a physician as an outcome assessor blinded to the participants' allocation and will assess the ADAS-Cog at baseline, three months, and six months. Recruitment will be done in the participant's native language.

Social media, such as Facebook, Instagram, X, and WhatsApp, will also be utilized, with preferences given to the most used social media in each area where recruitment centers are located.

To minimize the caretaker burden, incentives will be given as free transportation to and from the site where the OT training will be offered. Phone calls will be performed weekly to enhance adherence and to monitor follow-up on the homework assignments.

Adherence will be monitored through weekly phone calls by study nurses and by taking pictures of the group OT sessions and adding this to the log of each group exercise session. Monitorization of adherence will also be carried out on the control group through weekly phone calls.

Adherence in the control group is a more significant issue as this group will potentially show no effect from participation in the study. Therefore, for patients who complete the study without missing an OT session and especially for the control patients who meet the study without missing an outcome assessment, a pair of movie or dinner tickets will be issued at the end of the trial. Adherence to the cog-

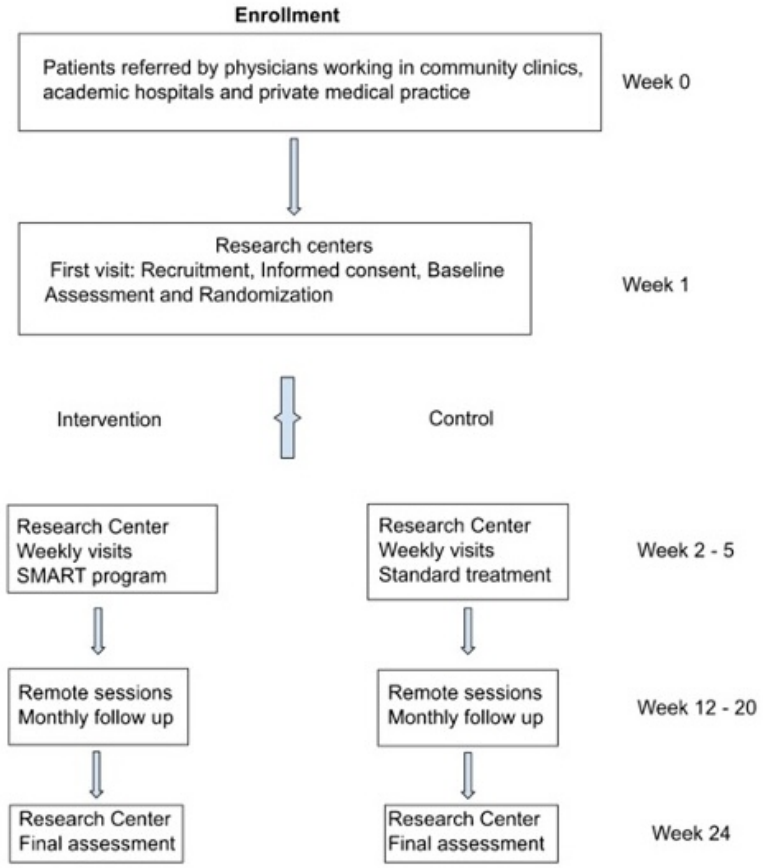

Figure 1: *SMART: Specialized Memory and Attention Rehabilitation Therapy program intervention.*

nitive OT will be evaluated by assessing encounter records with the physical therapist.

The SMART program is a cognitive rehabilitation intervention used for improving or maintaining cognitive functions in patients with mild Alzheimer's disease. The cognitive impairment will be assessed using the Alzheimer's disease assessment scale - cognitive subscale (ADAS-Cog). The ADAS-Cog is the most used rating scale in research for the progression of dementia. It is also considered the gold standard for assessing the efficacy of treatments for dementia (Kueper et al., 2018). It includes eleven tasks that assess cognitive domains of memory, language, and praxis. The tasks include subject-completed and observer-based assessments (Cano et al., 2010; Rosen et al., 1984).

This 5-week intervention is designed to have five joint sessions of 90 minutes (Figure 1).

The groups of the interventional arm will include a maximum of 6 participants based on the design of the SMART program (Griffin et al., 2022). Caregivers or family members will be encouraged to engage in each session, although participating will not be obligatory.

The occupational therapist will evaluate each participant individually at the beginning of the intervention to identify individual memory-related functional goals to work on during the group sessions. Also, in this personal first interview, the therapist will complete the assessments of the study.

An occupational therapist and a healthcare team member will form the facilitating team to support the activities.

The sessions will be provided in a standard healthcare or community center room on the same day of the week. Each session will last 90 minutes, and based on the SMART protocol, they will be defined by the following activities:

Week 1: Educational Visit "An introduction to dementia, brain health, and attention." This visit aims to educate the patient and family about the trial to assess patient characteristics by inclusion/ exclusion criteria. If accepted, informed consent will be filled in. This first visit will last approximately 30 minutes. The baseline assessment will also be done, and the patients will then be randomized according to the protocol.

Week 2: Baseline performance "Understanding memory," part I. The schedule will start the following week with weekly in-person visits during a 5-week program. Each week, the occupational therapist will individually assess the intervention group to identify

single memory-related functional goals and then participate in a group session (up to six patients) of 90 minutes consisting of the SMART program.

Week 3-4: "Home Environment, driving and future planning." After each session, patients will be encouraged to complete tasks at home related to implementing the memory strategies discussed and according to their personal goals. The 5-week program is detailed above.

Week 5: "Session recap". The control group will consist of pharmacological and behavioral intervention according to current American Psychiatric Association (APA) guidelines at the same frequency as the intervention group. After this initial period, both groups will be followed up by remote monthly maintenance sessions from the third to the sixth month of follow-up. Finally, at the end of the six months after randomization, there will be a last visit to do a final in-person assessment.

After each session, patients will be encouraged to complete tasks at home related to implementing the memory strategies discussed and according to their personal goals. At the beginning of each session, the facilitators will review the tasks performed by the participants. Also, each participant will receive a notebook for writing the tasks and their performance at home.

Both groups will receive the standard of care through their healthcare team.

Participants with a disease progression that can interfere with or make it impossible to continue with the SMART intervention will be discontinued from the study. Our clinicians will determine this on a case-by-case basis, and we will not assess this systematically.

Our primary outcome will be the mean change in cognitive function between groups measured by ADAS-cog from baseline to six-month follow-up.

Secondary outcomes include functional measures assessed by a client-centered goal-setting scale, the Canadian Occupational Performance Measure (COPM). Through a semi-structured interview, the patient identifies occupational performance problems experienced in everyday living and rates the level of performance and satisfaction in each one with a 10-point scale — one indicates poor performance and low satisfaction, whereas 10 indicates excellent performance and high satisfaction. Different assessments of COPM over time (baseline, three months, and six months) will detect changes in the client's self-perception of occupational performance (Aging, 2022).

Research assistants will enter and store all data using research electronic data capture REDCap with full HIPAA compliance. Access will be made password-specific for each center and collaborator. The sponsor will provide the dataset and the program for statistical analysis.

According to the Guidance for Clinical Trial Sponsors from the Food and Drug Administration, the trial does not meet the criteria of increased risk for participants since the study evaluates a purely behavioral intervention, and occupational therapy has been safely used in patients with AD thus far. Study investigators will evaluate data for potential adverse events experienced by study participants.

An interim analysis will not be necessary in our study. All patients will receive the standard of care; thus, we are not withholding proven treatments from patients. OT has been safely used in AD patients for other indications (Smallfield & Heckenlaible, 2017). Therefore, an interim analysis is not needed to evaluate the need to discontinue the trial due to adverse effects or the overwhelming superiority of one arm.

Based on previous data (Podhorna et al., 2016), the baseline ADAS-cog 13 in mild Alzheimer's disease was 29.91 (SD: 7.44). After six months of standard-of-care treatment, the ADAS-cog in the same patients was reported as 31.86 (SD: 8.61), representing a mean change of ADAS-cog of 2.1 (SD: 4.79). For our intervention, we hypothesize that we will not find a stable ADAS-cog, which means a mean difference of 0 (SD: 4.79). Using this data, we calculated the sample size by applying an alpha of 0.05, a power of 90%, and a drop-out rate of 20%, reaching 278 participants and 139 patients per arm.

Quantitative data will include central tendency measurements, including mean, median, standard deviation, and interquartile range. Qualitative data will be summarized with proportions and percentages. For the primary outcome, the mean change of ADAS-Cog after six months, we will test the normality distribution of the data with the Shapiro-Wilk test and histograms. Depending on the result of the normality assessment, we will perform a t-test or a Mann-Whitney test to compare the mean change between the experimental and control groups at the end of the OT intervention. To compare changes in ADAS-Cog subcategories, we will perform a chi-squared test. In addition, we will perform a paired t-test or Wilcoxon signed-rank test to compare differences (baseline vs endpoint) in scores between experimental and control groups separately. In the case of secondary outcomes, the functional score "client-centered goal setting scale," the "Canadian Occupational Performance Measure (COPM)," and "quality of life" (QOL) are going to be managed as continuous and ordinal data so we will perform t-tests and chi-squared tests accordingly. For all primary and secondary outcomes analyses, we will report p-

values and confidence intervals. We will consider a significant difference if $p < 0.05$.

Considering all randomized subjects, the study outcomes will be analyzed under the "intention-to-treat" (ITT) approach. We will report reasons for missing data for each randomized group and compare the explanations qualitatively. We expect missing data to fall in the "missing at random" category because our co-variables are not directly correlated with our outcomes. We intend to complete the dataset for missing data above 5% using the multiple imputation method. Subjects with missing data thus imputed will be included in the completed dataset, which will be analyzed according to the ITT approach.

We will perform a linear regression analysis to understand the effect of covariates on our primary outcome.

Discussion

The DECREASE trial is designed as a randomized, controlled, multicenter, phase III superiority trial. This will be the first large sample study involving 278 subjects that assess the effects of a cognitive-focused OT program, i.e., the SMART program, on the primary outcome of decreased decline in cognitive functions (as measured by ADAS-Cog) in patients with early-stage Alzheimer's Disease. The subjects will be randomized 1:1 to the intervention and control groups; both groups will be given the standard of care that includes pharmacological and behavioral intervention according to current American Psychiatric Association (APA) guidelines (Rabins et al., 2007), with the intervention group additionally receiving the SMART program.

As the current standard of care, such as cholinesterase inhibitors for AD, only provides symptomatic relief, any evidence from our study on the slowing deterioration of cognition in AD through the addition of the SMART program to standard medical treatment would provide invaluable information on innovative and effective ways to manage AD in its early stages. This is important as evidence in the literature has shown that the rate of cognitive decline is associated with the progression of behavioral problems in AD (Singh & Sadiq, 2022), and behavioral disturbances constitute one of the most significant sources of caretaker burnout. Slowing down cognitive decline thus provides AD patients with more time to remain independent, thus decreasing the caretaker burden. In addition, non-pharmacological approaches like cognitive-focused OT also have the advantage of not having undesirable side effects commonly seen in drugs that affect the quality of life of patients with AD.

The strengths of the SMART program are that it is non-invasive, safe, and highly feasible. The nature of such content can be documented in booklets or leaflets and distributed widely, making SMART highly standardized, replicable, and accessible to occupational therapists and caretakers in different locations around the world. This differs starkly from more traditional forms of OT, where physical exercises vary from therapist to therapist, making standardization difficult. In addition, this program requires the AD patient to be actively involved during the therapy sessions. This will allow AD patients to be meaningfully occupied in their day-to-day activities and may provide them with a renewed sense of purpose, improving their quality of life. Finally, our large sample would further substantiate the evidence in the previous study that used SMART on only 58 subjects.

The limitations of our study are the lack of objective measures to evaluate changes in the brain that may correlate to changes in cognitive functions. Another potential limitation is the short follow-up. Nevertheless, this decreases the risk of dropouts (changes in residence). Lastly, our study is an open-label RCT, as blinding patients and caregivers through a sham OT in the control group will not be feasible. This may add confounding effects to the primary and secondary outcomes. Thus, there may be placebo effects due to the intervention group's awareness that they are doing an additional therapy other than standard care. Future research and development of evidence-based, objective measures are needed. Nonetheless, the outcome assessor will be blinded.

There is broad evidence of OT benefits in the functionality (Ham et al., 2021). However, there is not enough literature on the effect of OT on cognitive function (Álvarez et al., 2017). Therefore, our study will add information to determine the usefulness of cognitive-based OT in AD patient care. Demographic transition, where populations are growing older, increases the urgency to act and create policies to improve well-being among older adults. Our study will provide data for future studies and guidelines for this purpose.

Conclusion

In conclusion, AD is a public health emergency that needs to be promptly addressed. The DECREASE trial aims to assess the effectiveness of a cognitive-based OT intervention amongst AD patients with enough statistical power. This information will finally determine if OT-based intervention can decrease cognitive decline and whether it should be included in the standard of care for AD.

Author Contributions

Conceptualization, A.B., S.A., G.A., M.B., L.B., A.E., D.E. C.G., H.H., J.K., V.M., R.M., C.P., L.P., N.P., C.J.P., G.R., N.R., S.R., L.R-W., M.S., J.W., E.Y., S.Z.; methodology, A.B., S.A., G.A., M.B., L.B., A.E., D.E. C.G., V.M., C.J.P., L.P., G.R., L.R-W., M.S..; software, H.H., R.M., N.P., C.P., S.R.; resources, X.X.; data curation, X.X.; writing—original draft preparation, A.B., S.A., G.A., M.B., L.B., A.E., D.E. C.G., H.H., J.K., V.M., R.M., C.J.P., L.P., N.P., C.P., G.R., N.R., S.R., L.R-W., M.S., J.W., E.Y., S.Z.; writing— review and editing L.R-W.; project administration, N.P.. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

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