Study Design for REGEnLIFE Clinical Trial II: A literature-based discovery approach to photobiomodulation protocols

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January 26, 2024

Abstract

REGEnLIFE, a company specializing in photobiomodulation (PBM) treatments for Alzheimer's disease, completed its initial clinical trial and is preparing for a larger, subsequent trial. This paper outlines the study design for this second trial, with a specific focus on optimizing PBM configurations and treatment protocols, including treatment duration, session length, number of sessions, irradiance, and wavelength. To inform this design, we employed a literature-based discovery (LBD) approach. A comprehensive collection of relevant PBM papers was vectorized and analyzed using a Large Language Model (LLM) equipped with retrieval-augmented generation capabilities. This process facilitated the synthesis of existing knowledge and the identification of optimal PBM configurations and protocols. The outcome of this novel approach is a set of data-driven recommendations for the configuration and application of the PBM device, as well as the overall treatment protocol for the upcoming clinical trial. These recommendations aim to enhance the efficacy and efficiency of PBM treatment in Alzheimer's patients, potentially contributing to improved clinical outcomes.

1 Introduction

1.1 Background

Alzheimer's disease (AD), a debilitating neurodegenerative disorder, has been the focus of various innovative non-pharmacological interventions, including photobiomodulation (PBM) therapy. PBM, a light-based neurostimulation approach, has recently gained attention for its potential in treating neurological conditions like AD. REGEnLIFE, a pioneer in this field, conducted a pilot study to assess the safety, compliance, and efficacy of a brain-gut PBM therapy for mild-to-moderate AD patients.

1.2 Rationale for the Second Trial

The initial study by **Blivet:2022** a double-blind, randomized, sham-controlled trial, was conducted between 2018 and 2020 but ended prematurely due to the COVID-19 pandemic. Despite this, the study yielded promising results: PBM therapy was safe with manageable adverse events (AEs), high patient compliance (92.5), and indications of cognitive function improvement in PBM-treated patients compared to the sham group. These findings, although encouraging, necessitate further investigation in a larger and more diverse AD patient population. The limited scale and the premature conclusion of the first trial highlight the need for a more extensive and robust second clinical trial to validate these initial findings and explore the full potential of PBM therapy in AD treatment.

1.3 Objectives of the Current Study

Building on the insights from the first trial, the objective of the upcoming study is to establish a more definitive understanding of the efficacy of PBM in treating AD. This will involve refining PBM configurations and treatment protocols based on a literature-based discovery (LBD) approach. By vectorizing and analyzing a wide range of PBM literature using an advanced Large Language Model with retrieval-augmented generation, this study aims to optimize treatment parameters such as session length, number of sessions, irradiance, and wavelength. The ultimate goal is to design a second clinical trial that not only corroborates the safety and compliance findings of the first trial but also provides more conclusive evidence on the efficacy of PBM in improving cognitive functions in AD patients.

2 Methodology

This section outlines the methodology used to design the second clinical trial, focusing on the literature-based discovery (LBD) approach for identifying optimal photobiomodulation (PBM) configurations and protocols, and the proposal for the clinical trial's study design.

2.1 Literature-Based Discovery Approach

The LBD approach involved a systematic selection and vectorization of relevant PBM studies. Sources included literature cited in the original study, reports from an external Contract Research Organization (CRO), as well as the arXiv dataset of 1.7m+ research papers. These papers were vectorised using HuggingFace embeddings and integrated into the Chroma DB database. To analyze this vectorized data, a retrieval-augmented generation (RAG) pipeline was set up, incorporating Mistral and the GPT-4 API. This RAG pipeline was designed to enhance the capabilities of the Large Language Model (LLM) in retrieving and synthesizing information from the vector database, thereby facilitating a more informed and comprehensive analysis of the literature.

2.2 Identification of Photobiomodulation Configurations and Protocols

The LLM agents were tasked with formulating queries to interrogate the vector database. These queries were based on specific research goals and parameters relevant to PBM treatment for Alzheimer's disease. The RAG pipeline produced pertinent vector embeddings in response to these queries, which the agents used for further investigation. Through an iterative cycle of query formulation, data retrieval, and analysis, a proposal for PBM configurations and protocols was developed.

3 Study Design Proposal for Clinical Trial

The proposed study design for the clinical trial incorporates the findings from the LBD process. Key recommendations include:

- Combining wavelengths of 820-850 nm and 1060-1070 nm to optimize light penetration and therapeutic effect.
- Increasing irradiance
- Adjusting session length
- Following a protocol of daily sessions extended over a longer total treatment period to maximize treatment exposure and potential therapeutic benefits.

An example implementation of the suggested configurations:

	Duration, Session	**Applications**	**Duration, Treatment**	**Wavelength**	**Irradiance**
Track 1.1	12.5 minutes	160	16 weeks	850nm	21.36 mW/cm2
Track 1.2	6 minutes	320	16 weeks	850nm	21.36 mW/cm2
Track 2.1	12.5 minutes	160	16 weeks	850nm + 1060-1080nm	21.36 mW/cm2
Track 2.2	6 minutes	320	16 weeks	850nm + 1060-1080nm	21.36 mW/cm2
Track 3.1	12.5 minutes	160	16 weeks	850nm + 1060-1080nm	42.72 mW/cm2
Track 3.2	6 minutes	320	16 weeks	850nm + 1060-1080nm	42.72 mW/cm2

These proposed configurations and protocols are designed to enhance the efficacy of PBM therapy in treating Alzheimer's disease, building upon the insights from the first clinical trial and the extensive literature analysis.

4 Discussion

This section interprets the findings from the literature-based discovery, discusses their potential impact on the upcoming clinical trial, and acknowledges any limitations and challenges.

4.1 Interpretation of LBD Findings

The literature-based discovery process, augmented by advanced LLM technology, provided a unique insight into the optimal configurations and protocols for photobiomodulation (PBM) in treating Alzheimer's disease. The recommendations for wavelength, duty cycle, irradiance, session length, and treatment duration are grounded in a comprehensive analysis of existing research. This approach ensured that the proposed trial design is informed by the most current and relevant data, potentially enhancing the efficacy and precision of PBM therapy in clinical settings.

4.2 Potential Impact

The upcoming clinical trial, guided by these refined PBM parameters, has the potential to significantly advance the field of non-pharmacological treatment for Alzheimer's disease. By systematically exploring the effects of different wavelengths, pulsations, and treatment durations, the trial could provide valuable insights into the mechanisms and effectiveness of PBM. This could lead to more targeted and effective treatments for AD patients, contributing to a higher quality of life and better management of the disease.

4.3 Limitations and Challenges

While the LBD approach using LLM technology is innovative and powerful, it is important to acknowledge its limitations. The quality of the findings is dependent on the existing literature, which may have gaps or biases. Additionally, the translation of these findings into a clinical trial involves inherent uncertainties. The actual impact of the recommended PBM configurations and protocols will need to be empirically validated in the clinical setting.

Furthermore, the implementation of a more complex and varied treatment protocol, as suggested by the LBD findings, may pose logistical and compliance challenges in a clinical trial setting. Ensuring consistent application of the treatment and monitoring for any unforeseen effects will be crucial.

5 Conclusion

The development of this study design for the second clinical trial on photobiomodulation (PBM) therapy for Alzheimer's disease (AD) represents a significant step forward in the intersection of advanced data analysis techniques and clinical research. Utilizing a literature-based discovery (LBD) approach, enhanced by a retrieval-augmented generation pipeline integrating Large Language Models (LLMs), has allowed for a data-driven and comprehensive exploration of PBM configurations and protocols.

The proposed trial, informed by this innovative methodology, aims to build upon the promising results of the initial pilot study. By refining treatment parameters such as wavelength, irradiance, session duration, and treatment frequency, this trial seeks to optimize the therapeutic potential of PBM in AD patients. The methodological rigor and the use of cutting-edge technology in this study design not only enhance its scientific validity but also demonstrate the evolving nature of clinical research in the digital age.

The outcomes of this trial could have far-reaching implications for the treatment of Alzheimer's disease. If successful, the trial could contribute to establishing PBM as a viable, non-pharmacological treatment option for AD, potentially improving the quality of life for patients and offering a new avenue for managing this challenging condition. Moreover, the use of LBD and LLMs in this study design may serve as a model for future clinical trials, showcasing the power of integrating artificial intelligence and machine learning in medical research.

In conclusion, this study design embodies the innovative spirit of combining traditional clinical research with advanced analytical tools. It stands as a testament to the potential of interdisciplinary approaches in addressing complex medical challenges and paves the way for future explorations in the realm of Alzheimer's treatment and beyond.

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