

Proposal for Lifestyle Intervention Clinical Trial: A Comprehensive Approach to Reversing Biological Age

Title:

"Multi-Modal Lifestyle Intervention to Reverse Biological Aging and Promote Longevity: A Randomized Controlled Trial"

Principal Investigator:

Dr. Stephen C. Rose, Ph.D.

Department of Nanoscale Engineering, SUNY Albany, Albany, NY

Advisory Role:

Dr. George Kuchel, gerontology expert with extensive experience in aging research, will serve as an advisory board member, offering insights on study design, clinical applications, and data interpretation.

Funding Mechanism:

SBIR (Small Business Innovation Research) Phase I and II Funding

- **Phase I (R43):** Initial funding to establish feasibility, assess preliminary efficacy, and gather initial data on the impact of the multi-modal intervention on biological age markers.
 - **Phase II (R44):** Expansion of the study with a larger participant pool and extended follow-up to comprehensively evaluate the intervention's efficacy and prepare for commercialization. The **National Institute on Aging (NIA)**, within the NIH, would be a targeted sponsor for this project due to its focus on aging research.
-

Industry Partnerships

1. TruDiagnostic: TruDiagnostic brings cutting-edge expertise in DNA methylation-based biological age analysis and will be the primary partner for measuring the intervention's impact on biological aging. Utilizing validated DNA methylation clocks such as Horvath, GrimAge, and PhenoAge, TruDiagnostic provides robust, precise measures of biological age, allowing for reliable tracking of epigenetic changes throughout the study. Their insights and analysis tools will be instrumental in assessing the intervention's efficacy in slowing or reversing biological aging.

2. Central Drugs Rx (Dr. Nayan Patel): Central Drugs Rx, under the direction of Dr. Nayan Patel, specializes in pharmaceutical compounding and personalized supplementation. They will be responsible for creating custom nutraceutical formulations designed to support key elements of the intervention, such as methylation processes, stress resilience, and mitochondrial health. Central Drugs Rx's tailored approach ensures that each participant receives supplements optimized for

bioavailability and efficacy, enhancing adherence and maximizing the potential health benefits of the intervention.

3. Apple Health: As a leader in health technology, Apple Health will play a critical role in collecting and integrating real-time health data through its platform. The Apple Health ecosystem will serve as the central data hub for monitoring participants' metrics related to sleep, physical activity, heart rate variability (HRV), and dietary adherence. By leveraging the Apple Health platform's advanced data analysis capabilities, we can track adherence patterns, assess intervention impact, and provide participants with personalized feedback based on real-time data. Apple Health's seamless data sharing and user-friendly interface enhance participant engagement, allowing for a holistic view of each participant's progress and enabling the study team to make timely adjustments to optimize outcomes.

4. YO-1 (Yovan Longevity Resort): YO-1, also known as the Yovan Longevity Center, is a potential partner in expanding and developing a wellness clinic aligned with the study's findings and intervention protocol. The Yovan Longevity Center specializes in integrative wellness, providing a natural fit for scaling the multi-modal lifestyle intervention into a clinical and resort-based setting where participants can access ongoing support and immersive wellness experiences. By partnering with YO-1, the trial results and intervention protocol could be translated into a comprehensive wellness program accessible to a broader audience, facilitating commercialization and expanding the reach of longevity-focused lifestyle practices. This partnership provides an avenue for long-term sustainability and scalability of the intervention, positioning it within a clinical wellness framework emphasizing holistic health and age management.

These industry partnerships create a robust infrastructure for the trial, blending scientific rigor with real-time tracking, personalized supplementation, and potential scalability into a wellness clinic format. Each partner contributes uniquely to the study's goals, supporting data integrity, participant adherence, and translating research findings into sustainable, real-world applications.

Research Team:

- **Principal Investigator:** Dr. Stephen C. Rose, an expert in nanotechnology and cellular aging research, will lead the study design, protocol development, and data analysis.
- **Research Collaborators:**
 - Dr. Leonard Hayflick, UCSF, renowned for foundational work in cellular senescence
 - Drs. Donald David Haines and Fadia Mahmoud, Advanced Biotherapeutics Ltd, specializing in immunology and anti-aging research
 - Dr. H. Robert Silverstein, Medical Director of Preventive Medicine Center, focusing on integrative health
 - Dr. Ray Yutani, Family Medicine, Western University, contributing expertise in clinical intervention design

- Dr. Nayan Patel, Central Drugs Rx, leading custom supplementation efforts for study participants
-

Background and Rationale:

Building on promising findings from the TRIIM trial by Greg Fahy and team—which demonstrated potential reversal of biological age using pharmacologic interventions such as growth hormone and metformin—this study seeks to replicate and expand these effects using a non-pharmacologic, lifestyle-based approach. The TRIIM trial faced limitations, including a small sample size, homogenous demographics, and reliance on drugs with limited applicability for the general population. This proposed study addresses these weaknesses by implementing a multi-modal lifestyle intervention to reverse biological age, measured by DNA methylation clocks, and to improve comprehensive health markers.

Hypothesis:

Primary Hypothesis: A structured, multi-modal lifestyle intervention, integrating dietary changes, exercise, stress reduction, and targeted supplementation, will result in measurable reductions in biological age markers (assessed via DNA methylation clocks), thus promoting longevity.

Secondary Hypothesis: The intervention will yield significant improvements in metabolic, cardiovascular, immune, and cognitive health, creating a holistic enhancement in quality of life and longevity.

Study Design:

- **Type:** Multi-center, randomized controlled trial (RCT)
 - **Duration:** 12-week intervention with follow-up assessments at 6 and 12 months to evaluate long-term effects.
 - **Sample Size:** 300 participants from diverse demographics to ensure broad applicability and robust data.
-

Participant Criteria:

Inclusion:

- Adults aged 40–65 with at least one risk factor for accelerated aging (e.g., poor diet, chronic stress, lack of exercise, or inadequate sleep).
- Willingness to undergo baseline and follow-up biological age testing via DNA methylation clocks.

Exclusion:

- Presence of chronic diseases that require active treatment which could confound results, or high-dose supplementation regimens that cannot be modified.
-

Intervention Components:

This intervention adopts a multi-modal approach to address various aging mechanisms identified in previous studies, incorporating diet, exercise, stress management, sleep optimization, and personalized supplementation.

1. Dietary Protocol:

- **Whole-Food, Plant-Forward Diet:** Emphasis on high intake of vegetables, fruits, nuts, seeds, and quality proteins.
- **Epigenetic Nutrients:** Daily supplementation with key methyl donors (e.g., folate, B vitamins), polyphenols, and adaptogens to support methylation and reduce inflammation.
- **Intermittent Fasting:** A 12-hour daily eating window to improve insulin sensitivity and metabolic health.

2. Exercise Regimen:

- **Zone 2 Aerobic Training:** Moderate-intensity aerobic exercise performed 4 times per week to improve cardiovascular health, mitochondrial function, and VO2 max.
- **Resistance Training:** Bi-weekly resistance exercises focusing on major muscle groups to prevent sarcopenia and support metabolic rate.

3. Stress Management:

- **Mindfulness Meditation:** Daily 15-minute mindfulness sessions to reduce cortisol levels, improve focus, and support mental well-being.
- **Yoga and Vagal Nerve Stimulation:** Three weekly yoga sessions incorporating breathing techniques to activate the parasympathetic nervous system.

4. Sleep Optimization:

- **Consistent Sleep Schedule:** Participants are instructed to maintain a regular sleep-wake schedule, exposing themselves to natural morning light and avoiding screens 2 hours before bedtime.
- **Controlled Room Environment:** Participants will receive blue-light blocking glasses and advice on creating a cool, dark sleep environment to improve sleep quality.

5. Personalized Supplementation:

- **Custom-Formulated Nutraceuticals:** Central Drugs Rx will provide individualized supplements, including adaptogens (ashwagandha), mitochondrial boosters (CoQ10), and anti-inflammatory agents (e.g., omega-3s, curcumin).

6. Regular Support and Monitoring:

- Weekly check-ins to support adherence, answer questions, and adjust protocols based on progress or personal needs.

Outcome Measures:

Primary Outcome

- **Reduction in Biological Age:** Using TruDiagnostic's Symphony Age platform, we will assess changes in biological age as measured by advanced DNA methylation clocks, including Horvath, GrimAge, PhenoAge, and TruDiagnostic's proprietary aging algorithms. This platform provides a nuanced view of biological aging, with actionable insights into the methylation patterns associated with various health outcomes. Assessments will be conducted at baseline, post-intervention (12 weeks), and follow-up intervals (6 and 12 months) to track the durability of intervention effects on biological aging.
- **Integration with Symphony Age for Actionable Insights:** TruDiagnostic's Symphony Age platform goes beyond biological age measurement by providing actionable insights on various aging pathways, such as inflammation, immune function, and metabolic health. Symphony Age will allow us to monitor methylation patterns in these areas, providing a deeper understanding of how the intervention influences specific biological pathways associated with aging. These insights will enable us to adjust and personalize the intervention protocols as needed, based on individual participant response.

Secondary Outcomes

The secondary outcomes will complement the primary measure of biological age reduction, examining broader health markers impacted by the intervention. TruDiagnostic's Symphony Age system will also contribute additional layers of data analysis and insights related to these health domains.

- **Metabolic Health:** Through metabolic pathway markers included in Symphony Age, we will assess changes in traditional metabolic health indicators, including fasting glucose, HbA1c, and lipid profiles. Symphony Age provides additional methylation-based insights into metabolic function, allowing for a more comprehensive evaluation of participants' metabolic health changes in response to the intervention.
- **Cognitive and Psychological Health:** Using PROMIS scales, we will evaluate mood, memory, and executive function using PROMIS scales. TruDiagnostic's platform includes

data on methylation sites associated with cognitive and psychological health, providing an epigenetic perspective on how lifestyle changes may influence cognitive resilience and emotional well-being over time.

- **Cardiovascular Health:** Improvement in cardiovascular fitness will be measured by VO2 max, blood pressure, and resting heart rate. Symphony Age includes methylation markers associated with cardiovascular risk, which will allow us to correlate physiological improvements with potential epigenetic shifts in cardiovascular health markers.
- **Immune Health:** To evaluate inflammation and immune system health, we will monitor changes in CD4/CD8 ratios, lymphocyte counts, and CRP levels. Symphony Age provides insights into immune system aging, capturing methylation changes linked to immune function and inflammation. This feature will enhance our understanding of how the intervention impacts immune resilience and inflammatory status, both key components of healthy aging.

Summary of Symphony Age Platform Benefits for the Study

TruDiagnostic's Symphony Age platform will allow us to go beyond traditional biomarker measurement by integrating epigenetic insights that reflect the participants' biological response to the lifestyle intervention. This approach will:

1. **Provide a Multi-Dimensional View of Aging:** Symphony Age enables a more complete assessment of the intervention's effects by examining age-related methylation patterns across several pathways (e.g., immune, metabolic, and cardiovascular).
2. **Enable Real-Time, Actionable Adjustments:** Symphony Age's actionable insights support personalized adjustments to the intervention protocol based on methylation responses, optimizing individual outcomes.
3. **Track Long-Term Epigenetic Shifts:** With follow-up assessments at 6 and 12 months, Symphony Age will help determine if the biological age reductions and pathway improvements are sustained over time, providing robust data for the intervention's long-term efficacy.

By integrating Symphony Age into the outcome measures, this trial can achieve a more sophisticated understanding of the intervention's biological and molecular impacts, supporting both immediate findings and future research on aging and longevity.

Exploratory Outcomes:

- Participant adherence, self-reported quality of life, and long-term behavioral changes after the intervention.
-

Data Collection and Analysis

Coordination with Apple Health and TruDiagnostic Platforms

Data collection, analysis, and management will be streamlined through coordinated integration with Apple Health and TruDiagnostic platforms. This collaboration enables seamless aggregation of participant data from multiple sources, including wearable devices, biological samples, and digital self-reports, into a centralized, secure system. The integration ensures real-time access to actionable data, enhancing the intervention's monitoring and adaptability.

Data Collection

1. Sample Collection:

- **Biological Samples:** Blood and saliva samples will be collected at baseline, after 6 weeks, at the end of the 12-week intervention, and during follow-up assessments at 6 and 12 months.
- **Epigenetic Analysis:** TruDiagnostic's Symphony Age platform will process and analyze DNA methylation patterns from these samples, providing a detailed assessment of biological age and pathway-specific aging markers.
- **Wearable and Self-Reported Data:** Through Apple Health, data on physical activity, sleep patterns, heart rate, and diet adherence will be continuously collected. Apple Health's secure data-sharing capabilities facilitate efficient data capture, allowing participants to upload information from wearables and daily logs automatically.

2. Data Integration and Management:

- Apple Health and TruDiagnostic's platforms will serve as a unified data repository, continuously synchronizing wearable data, epigenetic results, and other health markers. This integration streamlines data management, reduces the risk of data entry errors, and enables real-time monitoring of adherence and intervention impact.
 - Participants will have access to personalized dashboards to monitor their progress, which supports engagement and adherence to the intervention.
-

Data Analysis

1. Statistical Methods:

- **Mixed-Effects Regression Models:** Mixed-effects regression models will be applied to evaluate changes in biological age over time. These models account for repeated measures across time points, allowing us to assess individual responses to the intervention and track group trends.

- **Multivariate Analysis:** We will use multivariate analysis to explore relationships between lifestyle changes (as measured by wearable and self-reported data) and secondary health outcomes, such as metabolic, cardiovascular, and immune health markers.
- **Pathway-Specific Analysis:** TruDiagnostic's Symphony Age platform enables pathway-specific analysis, providing insight into how methylation changes in metabolic, immune, and cardiovascular pathways correlate with intervention outcomes.

2. Real-Time Data Monitoring:

- By using Apple Health's and TruDiagnostic's real-time data capabilities, we can assess adherence to the intervention protocols continuously. Any deviations or trends in participant data can be identified and addressed promptly, allowing for timely intervention adjustments that optimize individual outcomes.

3. Longitudinal Data Assessment:

- The integration of Apple Health and TruDiagnostic data facilitates a longitudinal analysis, allowing for a comprehensive view of biological and behavioral changes over the course of the study. With follow-ups extending to 12 months, we will assess whether improvements in biological age and health markers are sustained, providing valuable insight into the long-term efficacy of the intervention.

This data infrastructure, supported by Apple Health and TruDiagnostic, enables a sophisticated and efficient approach to data collection and analysis. The real-time insights provided by these platforms enhance our ability to monitor, adapt, and evaluate the intervention, making this study a model of advanced, technology-driven clinical research in longevity and health optimization.

Data Collection and Analysis:

- **Sample Collection:** Blood and saliva samples will be collected at baseline, after 6 weeks, 12 weeks, and at follow-up intervals (6 and 12 months).
 - **Statistical Methods:** Mixed-effects regression models will evaluate changes in biological age, and multivariate analysis will assess the relationship between lifestyle changes and health markers.
-

Commercialization Strategy:

1. **Subscription-Based Lifestyle Program:** Based on positive results, the intervention will be offered as a structured, commercially available program, providing users with personalized lifestyle recommendations, dietary guidelines, and regular biological age assessments.
2. **Integration with TruDiagnostic Dashboard:** A user dashboard for tracking biological age and health metrics could be developed in collaboration with TruDiagnostic, allowing for continuous engagement and progress tracking.
3. **Healthcare Partnerships:** Collaborate with healthcare providers, wellness clinics, and insurance companies to promote the program as part of preventative health services. For example, YO1 is a state-of-the-art health resort located in the Catskill Mountains of upstate New York, set among 1,300 acres of lakes and pine forests. It focuses on holistic health through various wellness programs, including curative therapies, yoga, and meditation, aimed at promoting longevity and overall well-being.
4. **Customized Supplement Line:** In collaboration with Central Drugs Rx, offer a line of targeted supplements tailored to support healthy aging and marketed alongside the intervention program.