The Impacts of Multivitamin and Mineral Supplementation on Cellular Metabolism and Healthy Aging

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Principal Investigator: Anthony Molina, PhD

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: The Impacts of Multivitamin and Mineral Supplementation on Cellular Metabolism and Healthy Aging

Study Description: The goal is to determine the impact of multivitamin and mineral (MVM) supplementation on clinical and biochemical markers associated with healthy aging, with a particular focus on mitochondrial function and metabolism. Participants will be randomized into one of three treatment arms (placebo, MVM "GOLD" Blend, MVM "US CORE" Blend).

Objectives:

1. *Primary Objective*: Determine the impact of acute and long-term MVM supplementation on clinical and biochemical markers of healthy aging
2. *Secondary Objective:* Compare the effects of different nutrient blend compositions on clinical and biochemical markers of healthy aging

Endpoints:

1. *Primary Endpoint:* Measurement of fresh peripheral blood mononuclear cell (PBMC) respiratory capacity.
2. *Secondary Endpoint:* Platelet/monocyte/lymphocyte respiratory capacity, body composition, grip strength, submaximal graded heart rate, serum nutrient and metabolite levels

Study Population: The study cohort will consist of sedentary men and women aged 40–60-years old.

Phase: NA

Description of Sites/Facilities Enrolling Participants: UC San Diego is the only site conducting this study. Different functions will be carried out in specific locations on the UCSD campus. The Exercise and Physical Activity Resource Center (EPARC) is a fully operating exercise physiology laboratory within the Herbert Wertheim School of Public Health, on the UCSD campus. The Geroscience Clinical Research Facility and Lab are housed within the School of Medicine and located in the Clinical Research Facility (CRF) and the Stein Institute for Research on Aging, respectively.

Description of Study Intervention: The study cohort will consist of 150 sedentary men and women aged 40–60-years of age. The study design is a double-blind, three-arm, placebo-controlled randomized clinical trial. Participants will receive a daily oral tablet containing one of two possible formulations of vitamins and minerals or a placebo. The three groups will be MVM "GOLD" blend formula, the US Restage MVM "US CORE", and the placebo group. Specific formulations of the three tablets are detailed in the **2025 Stability Provisional Expiry for Centrum Gold Blend Tablets (FN-2492-0001), Centrum US Restage Blend Tablets (FN-2493-0001, and Placebo of Centrum Gold Blend Tablets (FN-0436-0231) - Appendix 1: Table 1-1.** The participants will take the study product for 12 weeks.

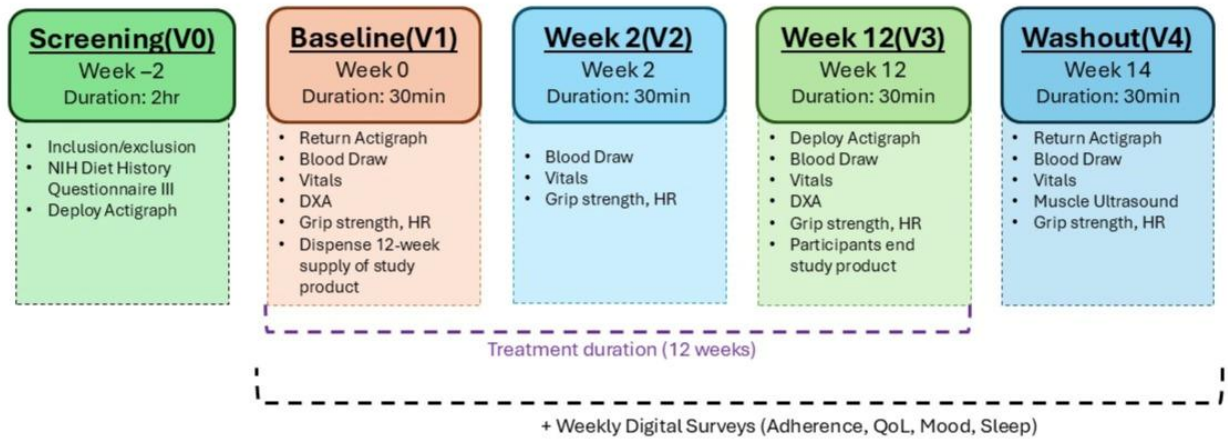
Summary of Study Visits: Data will be collected across five in-person visits spanning 16 weeks. The first visit (V0, Week -2) will involve screening and enrollment, nutritional assessment, and actigraph deployment. The baseline visit (V1, Week 0) will involve clinical measurements (blood draw, vitals, , grip strength, DXA, and submaximal heart rate), actigraph retrieval, and dispensing of the supplement.

An acute follow-up visit (V2, Week 2) will involve repeat clinical measurements, without the DXA. The last treatment visit (V3, Week 12) will involve repeat clinical measurements and a second actigraph deployment. After a two-week washout period, the final visit (V4, Week 14) will involve a final round of clinic measurementsand actigraph retrieval. Over the entire study period, weekly digital surveys of adherence, quality of life, mood, and sleep habits will be deployed.

Study Duration: 2 years
Participant Duration: 16 weeks

1.2 SCHEMA

Figure 1. Project Overview



1.3 SCHEDULE OF ACTIVITIES (SOA)

The prescreening and consent (V0) will occur prior to the completion of any assessment/intervention and will be 2 weeks prior to the initial assessment. As outlined in Table 1, all clinic-based measures will occur at Week 0, Week 2, Week 12, and Week 14. Physical assessments, described in detail below, will be performed at the Exercise and Physical Resources Center (EPARC) on the UCSD campus. In addition, individuals will be asked to provide a blood sample at each timepoint. Approximately 38-46 cc will be gathered by a licensed phlebotomist.

Table 1. Schedule of Activities (SOA)

Procedure	Screening (V0)	Baseline (V1)	W-2 (V2)	W-12 (V3)	Washout (V4)	Weekly Digital

	Week -2	Week 0	Week 2	Week 12	Week 14	Week 1-14
Informed consent	●					
Demographics	●					
Medical history	●					
Diet History Questionnaire III (DHQ III)	●					
International Physical Activity Questionnaire (IPAQ)	●					
Deploy wireless activity monitor	●			●		
Randomization	●					
Dispense 12-week supply of study intervention		●				
Daily supplement use		●	●	●		
Blood draw		●	●	●	●	
Complete blood count (CBC)		●	●	●	●	
Complete metabolic panel (CMP)		●	●	●	●	
Serum chemistry		●	●	●	●	
Vital signs		●	●	●	●	
DXA		●		●		
Grip strength		●	●	●	●	
Submaximal graded exercise test (GXT)		●	●	●	●	
Adverse Event Reporting		●	●	●	●	
Return wireless activity monitor		●			●	
Adherence log						●
Diet Quality Questionnaire (DQQ)						●
Warwick-Edinburgh Mental Well-being Scale (WEMWBS)						●
Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF)						●
Pittsburgh Sleep Quality Index (PSQI)						●

Table 2. Validated Surveys Administered at Baseline, week 2, week 12, and week 14

Survey	Domain(s) Tested	Description	Validation Reference
International Physical Activity	Physical Activity	Assesses 3 types of physical activity across 4 domains	Lee et al. 2011 (1)

Questionnaire- Short Form (IPAQ-SF)			
Diet History Questionnaire III (DHQ III)	Diet history and quality, nutrients, dietary constituents, and food groups	135 food and beverage line items and 26 dietary supplement questions	Subar et al. 2001 (2)
Diet Quality Questionnaire (DQQ)	Diet Quality	29 item (yes/no) survey to assess nutrient adequacy	Herforth et al. 2024 (3)
Warwick-Edinburgh Mental Well-being Scale (WEMWBS)	Positive affect (feelings of optimism, cheerfulness, relaxation), satisfying interpersonal relationships, and positive functioning (energy, clear thinking, self-acceptance, personal development, competence and autonomy)	14 items using a 5-point Likert scale (none of the time, rarely, some of the time, often, all of the time)	Tennant et al. 2007 (4)
Short Form Health Survey (SF-36)	Assessment of health-related quality of life	36 items evaluating physical functioning, role limitations, bodily pain, general health perceptions, vitality, social functioning, role limitations, and mental health.	Ware, Jr. JE, et al., 1992 (5)
Satisfaction, Alertness, Timing, Efficiency, and Duration (SATED	Assesses broad aspects of sleep health covering the five dimensions of sleep.	5 items covering sleep Satisfaction, Alertness, Timing, Efficiency, and Duration.	Buysse, DJ, et al. 2010 (6)
Pittsburgh Sleep Quality Index (PSQI)	Subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction	19 items	Buysse et al. 1989 (7)

2 INTRODUCTION

2.1 STUDY RATIONALE

The study goal is to determine the impact of MVM supplementation on clinical and biochemical markers associated with healthy aging, with a particular focus on mitochondrial function and metabolism. Specifically, high-resolution respirometry will be used to measure changes in mitochondrial respiratory capacity using peripheral blood mononuclear cells (PBMCs), as well as isolated platelets, monocytes, and lymphocytes. Blood-based bioenergetic profiling represents a minimally invasive approach for investigating mitochondrial function in humans that has been correlated with various other age-related markers of health such as physical function, gait speed, and resting metabolic rate (7, 8). It is hypothesized that MVM supplementation will impact the respiratory capacity of blood cells. The method in which MVM supplementation impacts other markers of health, including serum nutrient levels, metabolomic profiles, physical function, and skeletal muscle composition and quality will be explored. These comprehensive assessments will provide mechanistic insights into the potential benefits of MVM supplementation for healthy aging and address critical gaps in the current understanding of its acute effects. Further, this study will aid in the understanding of how multivitamin supplements can support heathy aging in mid-life adults, a key time to integrate proactive wellness solutions.

2.2 BACKGROUND

As the global population of older adults continues to expand, it is imperative to identify accessible and evidence-based interventions to support healthy aging. Among the key biological hallmarks of aging, mitochondrial dysfunction is highly modifiable and especially responsive to lifestyle interventions such as diet and exercise (9-11). Importantly, clinical studies demonstrate that mitochondrial bioenergetics plays a key role in the physical and cognitive abilities of older adults (12-15). Thus, identifying interventions that can improve mitochondrial bioenergetics is a promising avenue for the development of healthy aging interventions.

Multivitamin and mineral (MVM) dietary supplements have been used to support general health and nutritional status for years, particularly in older adults who are more susceptible to nutritional deficiencies due to factors such as reduced appetite, malabsorption, and polypharmacy. Observational studies consistently demonstrated that older adults exhibit higher rates of nutritional deficiencies, and that MVM supplementation may ameliorate these burdens (16). More recently, evidence suggests that MVM use may also confer functional health benefits; for example, the COSMOS-Mind trial demonstrated efficacy of MVM on global cognition, memory, and executive function in 2262 participants (17). Notably, most MVM studies are longitudinal and occur over the course of many years. A significant gap remains in understanding the acute effects of MVM supplementation on health and aging. Can rapid, measurable improvements in health be observed with MVM use? Moreover, what are the cellular mechanisms that can underlie the benefits of MVM use?

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The potential risks associated with study participation are deemed by the research team to be no greater than minimal.

MVM Supplementation

MVM supplements are generally considered safe with recommended use. Some potential risks listed on the product information page include:

- There is enough iron in the package to seriously harm a child. Close container tightly and keep out of reach of children. If taken accidentally, call a doctor immediately.
- Beta carotene should not be taken by smokers and those exposed to asbestos.
- Mega doses of Vitamin C may contribute to oxalate kidney stones and kidney diseases; it may also interfere with blood sugar test as it gives a false result.

https://www.haleonhealthpartner.com/en-sa/wellness/brands/centrum/products/adult-multivitamin/

Blood draw

The specific risk associated with the bioenergetic profiling strategy to be employed in this study is based on the drawing of blood. As with all blood draws, participants may experience temporary pain, bruising, bleeding and a small risk of infection or fainting or dizziness during the collection process. Only trained staff will be responsible for the collection of blood samples.

Physical Capacity Measurements

The participant may experience muscle fatigue and soreness due to the exercise tests performed in the study. The graded difficulty levels of the assessments are designed to probe an individual's true capacity; thus, there is a small risk of loss of balance during the graded exercise task.

Dual-energy X-ray Absorption (DXA)

The total amount of radiation projected for these scans of the spine, hip, and total body combined is up to 0.065 mSv (65µSv) for the largest participants. An average height non-obese individual is likely to take less than half of that exposure. Regardless of participant size, radiation exposure for the DXA scans is approximately 0.06965 mSv, which is less than what one would receive from one year of natural exposure in the San Diego area, which is approximately 1.6 mSv. However, since the long-term effects of exposure to a fetus are not known, pregnant women will not be scanned.

Risks of Interviews/Questionnaires/Quality of Life Assessments that Discuss Sensitive Issues

Participants may experience minor psychological anxiety due to the nature of the questionnaires.

Re-Identification

Participants providing biological specimens to the biobank risk re-identification of their samples should the security of the identification documents be breached. Proper storage and security of all samples and identification documents will be secured. Blood samples will be properly de-identified prior to transfer to laboratories for processing and repository storage.

Confidentiality

As with any study involving human participants, one potential risk is breach of confidentiality wherein a person's health status or other sensitive information might be disclosed, resulting in embarrassment, emotional distress, economic or other hardship, or prejudicial treatment by others.

2.3.2 KNOWN POTENTIAL BENEFITS

There will be no direct benefit to participants from this research.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Overall, the risks associated with the proposed study are minimal, manageable, and consistent with prior randomized trials involving MVM supplementation (COSMOS, PHS II, etc.). The potential knowledge gained about MVM supplementation on health and aging greatly outweighs the risks associated with the study. Risks will be managed as follows (in order of the risks presented above):

MVM Supplementation
To address the potential risks of multivitamin and mineral supplementation, the participants will be continually monitored for adverse events including gastrointestinal issues, allergic reactions, and drug interactions. Safety labs performed with each blood draw will also inform on potential adverse events. Participants will be provided with clear, understandable information about the potential risks and interactions, and will be encouraged to ask questions regarding the supplements and the study as a whole. The products will be manufactured by International Vitamin Corporation (IVC), in Greenville, South Carolina, according to GMP's, and sent directly to the study location to eliminate chances of adulteration or contamination.

Blood Draw
The specific risk associated with the bioenergetic profiling strategy to be employed in this study is based on the drawing of blood. With all blood draws, participants may experience temporary pain, bruising, bleeding and a small risk of infection or fainting or dizziness during the collection process. Only trained staff will be responsible for the collection of blood samples.

Physical Capacity Measurements
This protocol includes regular rest breaks to guard against muscle fatigue and soreness issues. The risk of loss of balance during the balance and gait tasks will be addressed through close supervision, observation, and communication.

Dual-energy X-ray Absorption (DXA)
To minimize exposure to radiation with the DXA scan, scans will only be conducted by highly skilled technologists certified by the state of California. These credentials help ensure correct subject positioning, selection of scan mode, and scan acquisition. This in turn minimizes the need for repeated scans and thus added radiation exposure. The measurement coordinator (DW) holds a Certified Bone

Densitometry Technician (CBDT) certification which is the ultimate level of technician training certification available.

Risks of Interviews/Questionnaires/Quality of Life Assessments that Discuss Sensitive Issues

Participants may ask to see the questions before deciding whether or not to take part in this study, and refuse to answer any specific questions that may make them uncomfortable. They will also be advised that they can withdraw from the study at any point and can still receive compensation. Similarly, clinical staff will review all data gathered during the physical examination and self-report measures.

Re-Identification

Proper storage and security of all samples and identification documents will be adhered to. Blood samples will be properly de-identified prior to transfer to laboratories for processing and repository storage.

Confidentiality

Strict confidentiality will be maintained. All members of the investigative team have completed the CITI Programs Good Clinical Practice and Biomedical Training Research Courses and are trained regarding the protection of participants' rights to confidentiality. They are required to successfully complete training according to standards of the HIPAA, and to complete the UCSD certification requirements. Project staff will be trained extensively to conduct all measurements accurately and respectfully. All participant data will be de-identified by assigning each participant a Unique ID in computer files. All data will be kept in a secure, locked office and only accessible to select study staff as detailed below in Item 16, Privacy and Confidentiality Considerations Including Data Access and Management. The study log with names and study identification numbers will be kept separate from the data and password protected.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Determine the impact of acute and long-term MVM supplementation on clinical and biochemical markers of healthy aging	• PBMC respiratory capacity measured at Weeks 0 and 12 • Serum concentration of dietary nutrients (vitamins D, B12, B6, E, C, and beta carotene) measured at Weeks 0 and 12	Previous investigations suggested that MVM supplementation may have an impact on blood cell bioenergetics and nutrient biomarkers (18).
Secondary		
Compare the effects of different nutrient blend compositions on clinical and biochemical markers of healthy aging	• PBMC respiratory capacity measured at Weeks 0 and 12 • serum concentration of dietary nutrients (vitamins D, B12, B6,	MVM reformulations are critical to maintain up-to-date scientific standards and meet evolving nutritional

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	E, C, and beta carotene) measured at Weeks 0 and 12	needs. Evaluation of the same primary endpoints in different MVM blends.
Tertiary/Exploratory		
1. Assess the impact of MVM supplementation on respiratory capacity of other cell types 2. Assess the impact of MVM supplementation on measures of physical function (grip strength, submaximal graded heart rate) and muscle composition (vastus lateralis muscle thickness, area, and intramuscular adipose tissue %). 3. Assess the impact of MVM supplementation on inflammatory markers. 4. Assess the psychosocial impact of MVM supplementation on measures of mood, quality of life, and sleep. 5. Explore the impact of MVM supplementation on changes in lipid metabolome. 6. Compare all outcomes between two different MVM blends that contain a unique nutrient profile.	• Platelet, monocyte, lymphocyte respiratory capacity • Grip strength, submaximal graded heart rate, and muscle composition (vastus lateralis muscle thickness, area, and intramuscular adipose tissue %) • Inflammatory markers • Mood, quality of life, and sleep • Lipid metabolome • All measured at Weeks 0, 2, 12, and 14	In addition to serum biomarkers, we are interested in potential clinical changes associated with MVM use. We chose quick, low-burden assessments of physical function to assess short-term impacts of MVM. Weekly surveys will also allow us to probe into any psycho-social changes.

4 STUDY DESIGN

4.1 OVERALL DESIGN

It is hypothesized that using multivitamin and mineral supplementation (1 pill/day) will result in both acute (2 week) and long term (12 week) changes in PBMC respiratory capacity and will increase the serum concentration of certain dietary nutrients (vitamins D, B12, B6, E, C, and beta-carotene) at 2 and 12 weeks. It is also hypothesized that a change in PBMC respiratory capacity and serum nutrient concentrations will be different between the two different MVM blends.

This study is conducted in the lab of Anthony Molina PhD, Division of Geriatrics, Gerontology, and Palliative Care, UC San Diego, and by the Exercise and Physical Activity Resource Center (EPARC).

Study Design: The study is a double-blind, three-arm, placebo controlled randomized clinical trial. The study cohort will consist of 150 (50 per arm) sedentary men and women aged 40–60 years

old. Participants will receive a daily oral tablet containing one of two possible specific formulations of vitamins and minerals while the placebo group receives a tablet with a similar appearance and taste but lacking active ingredients. Data will be collected across five in-person visits spanning 16 weeks. The first visit (V0, Week -2) will involve screening and enrollment, nutritional assessment, and actigraph deployment. The baseline visit (V1, Week 0) will involve clinical measurements (blood draw, vitals, , DXA scan), retrieval of the actigraph, and dispensing of the supplement. An acute follow-up visit (V2, Week 2) will involve the same clinical measurements, without the DXA. The last treatment visit (V3, Week 12) will involve the same clinical measurements and deployment of a second actigraph, to be collected after a two-week washout period in which one final round of clinical measurements (V4, Week 14) will be collected. Over the entire study period, weekly digital surveys of quality of life, mood, and sleep habits as well as a survey of adverse events will be sent out.

Location: Participant visits will be conducted at the UC San Diego Exercise and Physical Activity Resource Center (EPARC, http://www.ucsdeparc.org). EPARC is a state-of-the-science equipped recharge center specifically designed to offer the resources and expertise to conduct physical activity and exercise-related research. EPARC is comprised of a 2000+ square foot exercise physiology laboratory with resources that include, but are not limited to, a variety of accelerometers, HR monitors, and combined sensors. Researchers in many departments of UCSD's School of Medicine and School of Engineering, have previously used EPARC resources and services to measure participants for cross-sectional and longitudinal evaluation of health and response to intervention as well as to evaluate the validity of wearable and wireless sensors and related technologies and systems. EPARC staff includes physicians, exercise physiologists, nurses, epidemiologists, and educators. Dr. Molina serves on the EPARC Executive Committee and helps provide oversight of projects and facilities.

Blood processing, mitochondrial bioenergetic profiling, and biomarkers analyses will take place in the Geroscience Laboratory led by Dr. Molina. This lab is located in the Stein Clinical Research Building, which also houses the Stein Institute for Research on Aging and the Center for Healthy Aging. The research space comprises ~2000 sq feet of primary wet lab space and an adjacent 200 sq. foot cell/tissue culture room. A newly renovated space (243 sq feet) in the basement of the Stein Building has been assigned to Dr. Molina for metabolomics. The laboratory is exceptionally equipped for the conduct of mitochondrial bioenergetics research. These include multiple instruments from Agilent/Seahorse and Oroboros Instruments for analyzing cellular and mitochondrial respiration. All research staff and trainees in Dr. Molina's laboratory receive extensive training in mitochondrial bioenergetics. Training includes courses in advanced mitochondrial bioenergetics and high resolution respirometry held in Europe and the US through Mitochondrial Physiology Training Schools and intensive workshops focused on various applications of respirometry. Dr. Molina participates in many of these courses as an Invited Lecturer.

Recruitment and enrollment: Participants of the Successful Aging Evaluation (SAGE, PI: Molina, IRB# 171635) study at the University of California San Diego will be recruited. In addition, electronic and mailed announcements in the Stein Institute for Aging Research newsletter, university listservs and websites will be used. This cohort will be recruited through print advertisements in the local community.

The flyer contains basic information about the study and eligibility, as well as contact information for enrollment. There is also a QR code that will lead potential participants to a screening survey through which they can answer questions regarding eligibility and learn more about the study. Both the recruitment flyer and the screening survey are included in the IRB submission.

Inclusion/Exclusion Criteria:

Inclusion

1. IPAQ-SF categorical score of low or moderate physical activity (indicating sedentary lifestyle).
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Between 40-60 years of age
4. BMI ≥18.5 and ≤32 kg/m2
5. Weight stable for the prior 6 weeks

Exclusion:

1. Is pregnant or nursing.
2. Current smoker.
3. Diabetes (FPG > 180 mg/dL or A1c>8)
4. Heart or cardiovascular condition, including coronary artery disease, congestive heart failure, diagnosed abnormality of heart rhythm, atrial fibrillation and/or a history of myocardial infarction
5. Cancer or history of cancer within the past 5 years
6. Sensory or physical impairment that would prevent participation
7. Parkinson's disease, multiple sclerosis or other neurological condition, including a previous stroke, that may be causing impaired muscle function or mobility
8. Consistent use of any multivitamin and mineral supplement use, or any supplement that may interfere with measurements or biological outcomes (including but not limited to: NAD+ supplements, MitoQ)
9. Individuals with drug interactions as determined by the study physician

Randomization: Eligible participants will be randomized into one of three treatment arms (placebo, MVM “GOLD” Blend, MVM “US CORE” Blend). A stratified permuted block randomization approach will be used, in which participants are assigned to a block by sex (male or female), then randomized to treatment groups.

Supplements: Participants will receive a bottle containing the full 12-week treatment supply (84 pills). Participants will either receive placebo, MVM “GOLD” blend, or MVM "US CORE” blend based on their randomization. Both participants and providers will be blinded to the treatment arms. Supplements will be supplied by the study funder, Haleon.

Primary Endpoints: Fresh PBMC respiratory capacity, serum nutrient levels

Secondary Endpoints: Platelet/monocyte/lymphocyte respiratory capacity, muscle ultrasound (muscle thickness, area, intramuscular adipose tissue %), grip strength, submaximal graded heart rate.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

A placebo control will be used to establish a comparison standard on which to evaluate the efficacy of the multivitamin’s unique formulations. In this way, the effects of the experimental treatment can be isolated from natural health changes and the “placebo effect”.

4.3 JUSTIFICATION FOR DOSE

There are no new ingredients provided in either the MVM “GOLD” blend formula or the US Restage MVM "US CORE” formulas– they are simply versions of existing marketed product, Centrum Adults, but with lower vitamin/mineral dosages. Comparisons are outlined in **2025 Stability Provisional Expiry for Centrum Gold Blend Tablets (FN-2492-0001), Centrum US Restage Blend Tablets (FN-2493-0001, and Placebo of Centrum Gold Blend Tablets (FN-0436-0231) - Appendix 1: Table 1-1.**

Centrum is the world’s most clinically studied multivitamin brand with product usage (Centrum Silver) in large clinical trials such as The Physician’s Health Study II, AREDS I/II, The Italian-American Eye Study, and COS. Centrum formulas continuously undergo reformulation to incorporate the latest scientific advancements and address evolving nutritional needs. Ingredients are adjusted based on new research and clinical evidence, as well as consumer insights. This ongoing process ensures that Centrum products remain effective and relevant, providing consumers with the most up-to-date and beneficial multivitamin formulations available.

As such, the US Restage formula, identified as MVM "US CORE” Blend in the current study, is a modification to currently marketed Centrum Adult in which select nutrients have been removed or lowered to provide a better consumer experience (Section 6.2.2). Similarly, because Centrum is a global multivitamin/multimineral brand, it has numerous product formulations for different regions/markets around the world. To better harmonize these formulations across key markets, a ‘core’ blend of vitamins and minerals has been designed at levels that can be leveraged across different markets – this is internally being referred to as the MVM “GOLD” Blend formula (Section 6.2.2). The MVM “GOLD” Blend

formula will be a blend universally used as the base for Centrum tablets globally. These two new formulations and their impact on markers of healthy aging in mid-life adults will be addressed. There is a knowledge gap in understanding how a low-cost, safe, and easy wellness solution could proactively benefit individuals before more pronounced effects of aging begin to manifest.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study up to the final visit (V4, Week 14).

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

1. IPAQ-SF categorical score of low or moderate physical activity (indicating sedentary lifestyle).
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Between 40-60 years of age
4. BMI ≥18.5 and ≤32 kg/m2
5. Weight stable for the prior 6 weeks

5.2 EXCLUSION CRITERIA

1. Is pregnant or nursing.
2. Current smoker.
3. Diabetes (FPG > 180 mg/dL or A1c>8)
4. Heart or cardiovascular condition, including coronary artery disease, congestive heart failure, diagnosed abnormality of heart rhythm, atrial fibrillation and/or a history of myocardial infarction
5. Cancer or history of cancer within the past 5 years
6. Sensory or physical impairment that would prevent participation
7. Parkinson's disease, multiple sclerosis or other neurological condition, including a previous stroke, that may be causing impaired muscle function or mobility
8. Consistent use of any multivitamin and mineral supplement use, or any supplement that may interfere with measurements or biological outcomes (including but not limited to: NAD+ supplements, MitoQ)
9. Individuals with drug interactions as determined by the study physician

5.3 LIFESTYLE CONSIDERATIONS

Not Applicable.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but do not meet the inclusion/exclusion criteria and are thus not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demographics, screen failure details, eligibility criteria, and any serious adverse event (SAE).

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Study intervention will consist of three treatment arms (2 active multivitamin blends and an inactive placebo). See Table 3 and Table 4 for product ingredients.

- Centrum MVM “GOLD” Blend:
    - 17-ingredient blend of vitamins and minerals
    - 1 pill x 7 days/week x 12 weeks = 84 pills/bottle x (50 participants + 20%) = 84 pills/bottle for 60 participants (5,040 pills)
- Centrum MVM "US CORE” Blend:
    - 22-ingredient blend of vitamins and minerals
    - 1 pill x 7 days/week x 12 weeks = 84 pills/bottle x (50 participants + 20%) = 84 pills/bottle for 60 participants (5,040 pills)
- Placebo:
    - 1 pill x 7 days/week x 12 weeks = 84 pills/bottle x (50 participants + 20%) = 84 pills/bottle for 60 participants (5,040 pills)

6.1.2 DOSING AND ADMINISTRATION

Eligible participants will be randomized into one of three treatment arms (placebo, MVM “GOLD” Blend, MVM “US CORE” Blend). The treatment arms will be labeled A, B, or C. The intervention will be deployed as described above in terms of the number of pills per bottle. Pill bottles containing each

treatment arm will be indicated with the label in 6.2.2. Participants will be instructed to take one pill daily throughout the 14 weeks of the study. Both participants and study staff will be blinded to the three treatment arms.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The intervention and control products will all be sent to the investigator from the manufacturer site, International Vitamin Corporation (IVC). The 3 treatment products will be delivered in bottles that appear similar to currently available Centrum multivitamins and will be labeled MVM-A, MVM-B, and MVM-C.

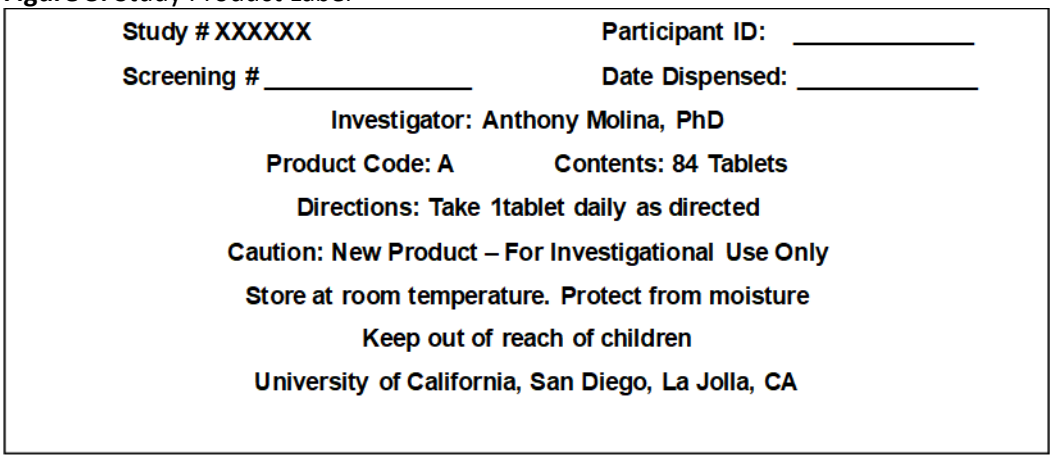
All products will be tracked using the Investigational Agent Accountability Record (attached), and any unused product will be sent back to the manufacturer for disposal.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The formulations of the 3 treatment products are listed in **2025 Stability Provisional Expiry for Centrum Gold Blend Tablets (FN-2492-0001), Centrum US Restage Blend Tablets (FN-2493-0001, and Placebo of Centrum Gold Blend Tablets (FN-0436-0231) - Appendix 1: Table 1-1**.

The treatment products will be delivered in identical bottles that appear similar to currently available Centrum multivitamins and will be labeled MVM-A, MVM-B, and MVM-C. Please see Figure 3 for example product label.

Figure 3. Study Product Label



6.2.3 PRODUCT STORAGE AND STABILITY

Active treatment and placebo products can be stored at normal room temperature. No special storage instructions will be required. Expiry information provided by Haleon indicates a tentative expiry term of 18 months, which is adequate for the current study duration. **2025 Stability Provisional Expiry for**

Centrum Gold Blend Tablets (FN-2492-0001), Centrum US Restage Blend Tablets (FN-2493-0001, and Placebo of Centrum Gold Blend Tablets (FN-0436-0231) - Table1-1

6.2.4 PREPARATION

All preparation of intervention and control products will be done by the manufacturer, International Vitamin Corporation (IVC). Study staff will only be responsible for dispensing the product according to random assignment.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Eligible participants will be randomized into one of three treatment arms (placebo, MVM "GOLD" Blend, MVM "US CORE" Blend). A stratified permuted block randomization approach will be used, in which participants are assigned to a block by sex (male or female), then randomized to treatment groups. Random assignment will be double blind, so randomization assignment and product labels will be MVM-A, MVM-B, and MVM-C.

6.4 STUDY INTERVENTION COMPLIANCE

Protocol adherence will be monitored and assessed using weekly self-reported adherence logs that will be administered electronically. Compliance will be classified as ≥ 80% adherence throughout the study period.

6.5 CONCOMITANT THERAPY

Participants who, during screening, report consistent use of any multivitamin and mineral supplement, or any supplement that may interfere with measurements or biological outcomes (including but not limited to: NAD+ supplements, MitoQ) will be excluded. Additionally, participants will be instructed to report to study staff whether they begin using any medications at any point during the study period. The medical history data collected at screening will include all medication use to be used in a potential sensitivity analysis investigating possible effects of concomitant medication use.

6.5.1 RESCUE MEDICINE

Not Applicable

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from Multivitamin and Mineral Supplementation study does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including but not limited to changes from

baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include final blood labs and scheduled follow-up questionnaires.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to take the dose of multivitamin for 3 consecutive days.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Multivitamin Study Case Report Form (CRF). Research participants who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Research participants who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 1 of the scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit up to 2 weeks following the expected visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of loss to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

The baseline study visit will occur at least 2 weeks after, but no more than 4 weeks after, the initial screening visit (actigraph will be deployed at screening and will be worn for 2 weeks).

At each study visit (V1, V2, V3, V4) the participant will undergo a fasted blood-draw followed by a snack break, assessment of vital signs, and physical assessments as listed below.

Sample Collection: A licensed phlebotomist will perform a venipuncture blood draw at the forearm, arm, or antecubital fossa of either arm and collect 20 ml of blood into three 10ml Acid Citrate Dextrose (ACD) tubes, one serum-separating tube (SST), and one ethylenediaminetetraacetic acid (EDTA) tube for each blood-draw visit (V1, V2, V3, V4). On visits V2 and V3, three additional ACD tubes for fresh cell assays will be collected. The previous studies indicate that samples are stable for 8 hours at room temperature.

Within 1 hour of sampling, the blood will be processed to separate blood components. Blood will be spun down and freeze platelets and PBMCs from all four blood-draw visits (V1-V4) for frozen respirometry. During V1 (baseline) and V3 (week 12) visits, additionally live cells will be isolated for fresh respirometry. Fresh respirometry will include platelets, PBMCs, monocytes, and lymphocytes.

Clinical Laboratory Measurements: Tubes of whole blood will be delivered to the UCSD Center for Advanced Laboratory Medicine (CALM) Labs as well as the Associated Regional and University Pathologists, Inc (ARUP) Laboratories in Salt Lake City, UT to run various blood tests, including: compete blood count, comprehensive metabolic panel, c-reactive protein, sedimentation rate, lipid panel, and serum levels of cortisol, vitamins D, B12, B6, E, C, and beta-carotene.

Assessment of Vital Signs: Measurements of height, weight, heart rate, and blood pressure will be administered by trained study staff.

Wireless Activity Monitor: Objective assessments of physical activity will be measured using the ActiGraph GT3X+ accelerometer (ActiGraph, LLC; Pensacola, FL). The GT3X+ is a lightweight (19g) triaxial solid state accelerometer, with a dynamic range of +/- 6g and a user-specified sampling rate of 30-100hz (in 10hz increments) (19). The device is approximately 2’’x2’x0.5’’ in size and is worn on the hip attached to a belt around the waist. The device has 512MB of non-volatile flash memory and a 3.7V prismatic lithium-ion battery allowing for 40 days of raw acceleration data to be collected at 30Hz.

A seven-step algorithm identified as best-practice for the collection, processing, and summarization of PA accelerometer data collected with wearable systems will be used (20). Wear time instructions will be provided, and a brief self-report wear time log for participants to note periods that the device was taken off. Participants will be asked to wear the ActiGraph for seven days and will be prompted twice via telephone during the monitoring period (wear days 2 and 5) to assist with compliance. Upon return,

information will be immediately downloaded as well as screen ActiGraph data by hour for completeness and possible irregularities/malfunction according to best practice recommendations (21).

Accelerometer outcome variables include (i) mean minutes per day of sedentary time, (ii) mean minutes per day of light intensity physical activity, and (iii) minutes per week of moderate-to-vigorous intensity physical activity (MVPA). Additional variables will also be computed based on patterns of how sedentary time and MVPA is accumulated (e.g., minutes of sedentary time per day occurring in bouts ≥30 minutes; minutes per week of MVPA occurring in bouts of ≥ 10 minutes).

Grip Strength: Hand grip strength will be measured in both hands using an adjustable grip strength dynamometer (BL5001 Hydraulic Hand Dynamometer). Participants will be allowed a chance to familiarize themselves with the measurement by making a submaximal effort on both hands to feel how the instrument will react. For the assessment, the participant will stand and hold the dynamometer in their hand with their arm down at their side. The participant will be instructed to take a deep breath in and squeeze as hard as possible as they exhale. The measurement will be repeated twice on each hand, alternating between each side, and the highest score for each hand will be recorded to the nearest kilogram.

Submaximal Graded Exercise Test: Submaximal Graded Exercise Test (GXT) on a treadmill will be conducted at EPARC under the supervision of a trained exercise physiologist. Participants will complete a walking protocol at a self-selected speed, with the treadmill incline increasing every two minutes to progressively increase cardiovascular demand. The test will continue until the participant reaches 85% of their age-predicted maximal heart rate (calculated as 220 bpm – age) or experiences volitional fatigue, whichever occurs first.

The test itself is expected to last approximately 5-10 minutes, excluding warm-up and recovery periods, with the total session lasting about 20 minutes. For the first visit (V1) blood pressure and heart rate before, during, and after the test, will be measured including at least five minutes into recovery and again before the participant leaves the lab. If there is a risk detected during blood pressure monitoring, (systolic >200, or an increase in diastolic during exercise), then BP monitoring will continue throughout all visits. For every visit, continuous heart rate monitoring will be performed via Polar chest strap, and ratings of perceived exertion (RPE) will be collected at regular intervals during the test.

In the unlikely event of a cardiac event or medical emergency, EPARC staff are trained in emergency procedures, and an automated external defibrillator (AED) and supplemental oxygen are available on-site. The protocol aligns with standardized exercise testing guidelines to provide reliable and meaningful physiological data while prioritizing participant safety.

Dual-energy X-ray Absorptiometry (DXA)

Bone Mineral Density/Content (BMD/BMC) and Body Composition

BMD/BMC and body composition will be assessed by dual energy x-ray absorptiometry (DXA) on a Prodigy Advance densitometer (GE/Lunar, Madison, WI). Densitometry will be performed by the same

technician certified by the State of California Radiologic Health Branch. The scan sites include the spine (L1-L4), proximal femur (femoral neck and total hip), and whole body. The DXA whole body scans will be used to determine whole body BMD/BMC as well as body composition (fat and fat-free mass, and %fat). The total time required for subject positioning and scanning of the spine and hip is about 5 minutes, and ~6 minutes for the total body, in standard scan mode. Radiation exposure for all 3 scans is approximately 8-10 µSv (0.8-1.0 mRem), which is approximately equal to a day of background exposure. Since the long-term effects of exposure to a fetus are not known, pregnant women will not be scanned. Quality assurance tests are performed each morning of testing. The mean coefficient of variation (% CV) in the laboratory, based on precision studies of 30 individuals measured twice on the same day is: 0.64% for the total hip, 1.39 for femoral neck, 0.82% for the spine (L1–L4), 0.85% for total body BMD, 1.89% for total body fat mass, and 0.7% for total lean mass.

Subject Preparation

Subjects are instructed, prior to the day of their scan, to dress in single-layer, loose clothing free of any metal, plastic, or similar materials, including all jewelry as well as leather or other dense fabrics. Women are encouraged to wear a halter-top or something similar. Subjects should be normally hydrated, and if they take a calcium supplement, not to take it on the day of their scan. Scans should not be done within 10-14 days following medical testing requiring any contrast agent.

Weekly Electronic Surveys: Weekly electronic surveys will be sent using REDCap. Electronic surveys will include the Diet Quality Questionnaire (DQQ), Warwick-Edinburgh Mental Well-Being Scale (WEMWBS), Short Form Survey (SF-36) quality of life survey, SATED sleep survey, and Pittsburgh Sleep Quality Index (PSQI) [sleep surveys are only administered monthly]. We will also ask participants to fill in an electronic adherence log each week to keep track of study compliance.

8.2 SAFETY AND OTHER ASSESSMENTS

Each week after the baseline visit (V1) the participant will electronically complete an adherence log. The log will be delivered along with the weekly electronic surveys described above. Further, safety labs from each blood draw will be monitored to ensure that the MVM supplementation does not cause any aberrant nutrient levels.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

The FDA definition of an Adverse event is any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

All adverse events (AE) based on the definition of 21 CRF 312.32(a) will be captured by study staff and reported to IRB and/or participant's physician as needed.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

The following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".]

In the context of this intervention, an allergic or other reaction may occur which would be unexpected and defined as an adverse event. In the event that this occurs in the laboratory and requires an emergency room visit, but not inpatient hospitalization, or injury sufficient for withdrawal from the study will be considered AE and reported accordingly.

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) will be reviewed by the study PI and the following determination of their relationship to the study will be determined. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the

study intervention (DE challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.]

8.3.3.3 EXPECTEDNESS

Anthony Molina, PhD and Benjamin Han, MD will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be recorded by study staff. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The study coordinator or EPARC study staff will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the study personnel will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

The PI, or study team under the direction of the PI will report all AE's to the IRB, and other UCSD regulatory bodies using the timelines described above.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study staff will immediately report any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the PI and other UCSD regulatory bodies.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the UCSD regulatory bodies and should be provided as soon as possible.

The studyPI will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the s's initial receipt of the information. In addition, the PI must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the PI determines that the information qualifies for reporting.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

There will be no informing participants of AE or SAE not related to themselves. New risks beyond those described above and relayed to participants during the consent process are not anticipated.

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable

8.3.9 REPORTING OF PREGNANCY

In the event that a participant becomes pregnant during the course of the study, they will be instructed to discontinue the study intervention, while continuing the safety follow-ups

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied.
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The study staff will report unanticipated problems (UPs) to the Institutional Review Board (IRB) andthe principal investigator (PI)in a timely fashion. The UP report will include the following timing guidelines:

- UPs that are serious adverse events (SAEs) will be reported to the IRB
- within 3 days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB at the time of continuing review in the event of a very minor UP, or within 14 days for UP's which may involve increased risk across the study population.
- All UPs should be reported to the Office for Human Research Protections (OHRP) following the same timelines described above.

The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;

- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

The study staff will inform participants about an unanticipated problem, provide details of the problem as well as potential implications for their safety and well-being. The information will include the steps being taken to mitigate the risks as well as any changes to the protocol. This communication will be made in person at their study visit, or via phone/email for more acute problems.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Primary Efficacy Endpoint(s):

- MVM supplementation will result in both acute (2 week) and long-term (12 week) change in PBMC respiratory capacity
- MVM supplementation will increase serum concentration of certain dietary nutrients (vitamin D, vitamin B, folic acid, magnesium, calcium, and iron) at 2 and 12 weeks

Secondary Efficacy Endpoint(s):

- Change in PBMC respiratory capacity and serum nutrient concentrations will be different between the two different MVM blends.

Exploratory Aims:

- Assess the impact of MVM supplementation on respiratory capacity of other cell types, including platelets, isolated monocytes, and isolated lymphocytes.
- Assess the impact of MVM supplementation on measures of physical function (grip strength, submaximal graded heart rate) and muscle composition (vastus lateralis muscle thickness, area, and intramuscular adipose tissue %).
- Assess the impact of MVM supplementation on inflammatory markers.
- Assess the psychosocial impact of MVM supplementation on measures of mood, quality of life, and sleep.
- Explore the impact of MVM supplementation on changes on the metabolome.
- Compare all outcomes between two different MVM blends that contain a unique nutrient profile.

9.2 SAMPLE SIZE DETERMINATION

Proposed sample size (n=150, 50 per arm) after attrition is adequately powered (1-β = .80) to detect a pairwise difference effect size = 0.56 using a 2-tailed α=0.05. Power calculations are based on independent t-tests and were conducted using G*Power 3.1.9.7.

For the primary outcome of PBMC maximal respiration, previous work by the study team indicates that an effect size of 0.5 for maximal respiration is equivalent to a difference of ~75 pmol/min of O2 consumption. A difference in respiration of 75 pmol/min is thought to be quite reasonable; in fact, previous work demonstrates that the average PBMC Max Respiration in the 30-40 age group is different than the 40-60 age group by about 75 pmol/min.

All secondary and exploratory analyses will use similar pairwise t-tests to compare differences between groups so power analysis

Interim analyses will be conducted at the study half-way point and used for sample size re-estimation. Blinded sample size re-estimation will use revised estimates of the outcome variance to re-calculate sample size and enrollment will be adjusted as needed.

9.3 POPULATIONS FOR ANALYSES

1. Primary analyses will use a Modified Intention-to-Treat dataset that includes all randomized participants who followed protocol through, and attended, the first 2-week follow-up.
2. Sensitivity analyses of a Per-Protocol dataset will be used to further investigate treatment efficacy. This dataset will include participants with treatment adherence ≥ 80% and attendance of at least one follow-up visit.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Preliminary statistics will include percentages, means, rates, correlations, measures of variance, and distribution characteristics of analytic variables. Variables that are non-normally distributed will be transformed or use distribution-appropriate approaches (e.g., Poisson distribution for count data). Data will be examined for the presence of outliers, and if found, outliers will be re-coded or omitted as appropriate. Baseline equivalence across study arms will be evaluated using chi-square tests for discrete data and ANOVA for continuous data. If a statistically significant difference is found, the variable(s) will be included as covariates in all subsequent analysis.

The primary study hypotheses (Primary Aims 1 and 2) will be tested using a modified Intent-To-Treat (ITT) approach utilizing linear mixed effects regression models (i.e., mixed models or generalized mixed models). This statistical approach accounts for the correlated nature of repeated measurements, allows maximum use of all available observations, and is robust to data Missing-At-Random (MAR). R packages lmer and nlme will be used as appropriate for the specific dependent variable. The statistical analyses will consist of the following pairwise treatment comparisons calculated from the random effects regression models (adjusted LSMEANS):

MVM “GOLD” Blend vs placebo at 2 weeks
MVM “US CORE” Blend vs placebo at 2 weeks
MVM “GOLD” Blend vs placebo at 12 weeks
MVM “US CORE” Blend vs placebo at 12 weeks

The results of the comparisons will be presented as estimated contrasts and 95% confidence intervals with two-sided p-values.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Primary Aims 1 and 2 are to determine the effect of daily MVM supplementation on PBMC respiratory capacity and serum nutrient concentrations. Both respiratory capacity and nutrient concentration levels are continuous values that will be measured repeatedly at baseline, 2-week and 12-week. We hypothesize that participants assigned to each active treatment arm (MVM "GOLD" Blend and MVM "US CORE" Blend) will show changes in PBMC respiratory capacity and serum nutrient concentration at 2-week and 12-week follow-up compared to participants assigned to the placebo arm. A linear mixed effects regression model with PBMC Maximal Respiration or serum nutrient capacity as the dependent variables, follow-up time as the random (within-subject) factor, and treatment assignment as the fixed (between-group) factor will be used. Any characteristic found to be different across randomization groups will be included as covariates. The hypotheses will be tested through the interaction effect of treatment by time, and as a main effect of treatment across the follow-up observations controlling for baseline differences. Marginal means will be presented as LSMEANS (SE) and will be pairwise tested using t-tests. Differences with p-values < .05 will be considered statistically significant. No adjustment will be made to the primary aim p-values as these hypotheses were defined a priori.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary Aim is to test whether the change in respiratory capacity or nutrient concentration differs between MVM "GOLD" Blend and US CORE Blend. It is hypothesized that the participants assigned to MVM "US CORE" Blend will show larger change in PBMC respiratory capacity and larger increase in serum nutrient concentrations than the participants assigned to the MVM "US CORE" Blend. The same model described in Primary Aim 1 and Primary Aim 2 will be used to construct the following pairwise treatment comparisons for PBMC respiratory capacity and serum nutrient concentrations of vitamin D, vitamin B, folic acid, magnesium, calcium, and iron.

MVM "GOLD" Blend vs MVM "US CORE" Blend at 2 weeks
MVM "GOLD" Blend vs MVM "US CORE" Blend at 12 weeks

Exploratory Analyses will use the methodology described above to further test pairwise treatment comparisons for all additionally collected data, including respiratory capacity of other cell types (platelets, isolated monocytes, and isolated lymphocytes), markers of physical function and muscle composition, psychosocial markers of mood, quality of life, and sleep, as well as metabolomic signatures. Results of all exploratory analyses will be presented with exact p-values to allow adjustment to control for family-wise Type-I error rate.

9.4.4 SAFETY ANALYSES

Not applicable. Although this study does not have any safety endpoints, adverse events will be continually monitored, as will serious adverse events and clinical lab parameters (ie, blood counts and blood vitamin levels).

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Preliminary statistics will include percentages, means, rates, correlations, measures of variance, and distribution characteristics of analytic variables. Variables that are non-normally distributed will be transformed or use distribution-appropriate approaches (e.g., Poisson distribution for count data). Data will be examined for the presence of outliers, and if found, outliers will be re-coded or omitted as appropriate. Baseline equivalence across study arms will be evaluated using chi-square tests for discrete data and ANOVA for continuous data. If a statistically significant difference is found, the variable(s) will be included as covariates in all subsequent analysis.

9.4.6 PLANNED INTERIM ANALYSES

Interim analyses will be conducted at the study half-way point and used for sample size re-estimation. Blinded sample size re-estimation will use revised estimates of the primary outcome variance to re-calculate sample size and enrollment will be adjusted as needed. Because interim analyses will only include statistical analysis of the primary endpoint, there will be no impact on the final efficacy analyses other than potential increased sample size.

9.4.7 SUB-GROUP ANALYSES

As exploratory analyses, subgroups based on sex and baseline activity scores will be analyzed.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual data will be maintained based upon participant ID for each measure at each timepoint.

9.4.9 EXPLORATORY ANALYSES

In addition to the primary analyses focused on the effects of multivitamin use on mitochondrial bioenergetics and overall efficacy of the intervention, exploratory analyses will be conducted to identify subgroups who may benefit the most from multivitamins.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the study participants and regulatory authorities by the PI, and the PI will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to the study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the PI and IRB.

10.1.2 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators andtheir staff. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the PI.

All research activities will be conducted in as private a setting as possible.

The study monitor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, or Institutional policies.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the <specify name of Data Coordinating Center>. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by <specify name of Data Coordinating Center> research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the <specify name of Data Coordinating Center>.

10.1.3 FUTURE USE OF STORED SPECIMENS AND DATA

Data and biological samples collected for this study will be analyzed in the Geroscience laboratory of Dr. Molina.De-identified bio-samples including serum, plasma, and blood cell components will be stored indefinitely in a biobank created in this Geroscience laboratory inside the Stein Clinical Research Building. The de-identified, archived data will be stored within REDCap. Identifiable study log will be

separate from the data and password protected, and physical consent forms will be kept in a locked cabinet and will be destroyed according to UCSD policy.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in the lab of Dr. Molina within REDCap. The study data entry and study management systems used by clinical sites and by the Molina study research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived within REDCap.

10.1.4 KEY ROLES AND STUDY GOVERNANCE

Anthony J.A, Molina, PhD (PI) is Professor of Medicine and Scientific Director of the Stein Institute for Research on Aging and the UCSD Center for Healthy Aging. He also serves as the Research Chief for the Division of Geriatrics, Gerontology, and Palliative Care. Dr. Molina is a Gerontologist and mitochondrial biologist with expertise in translational research and assay development.

Dr. Molina is responsible for the development of the multivitamin study curricula as well as the design, execution, management, and oversight of the blood-based analyses and long-term storage of residual blood and serum in his biorepository. Dr. Molina will work closely with study staff to ensure that the proposed project is completed safely and with the highest level of scientific integrity.

Address: 9500 Gilman Drive MC 0665, La Jolla, 92093

Phone: (858) 246-5930

Email: *ajmolina@health.ucsd.edu*

Benjamin Han, MD (Medical Safety): Dr. Han is a licensed geriatrician and will provide medical oversight for this trial. He will work with this study team to ensure the safety of all participants and will support the interpretation of clinical data.

Howard Phang (Research Staff): Mr. Phang is a PharmD/PhD student in Dr. Anthony Molina's Lab at UCSD. He serves as a primary liaison with the Haleon, the study funder. He will be assisting in the implementation of the study protocol, including blood processing and assessment of mitochondrial function.

Lina Scandalis, PhD (Program Coordinator) will coordinate operations related to the Multivitamin study. Dr. Scandalis will be responsible for processing blood samples and for conducting bioenergetic profiling experiments. In addition, Dr. Scandalis will be involved with screening and recruitment. Dr. Scandalis will

conduct regular meetings with study investigators and provide updates on progress towards project goals. Dr. Scandalis will interact with other scientists to ensure that samples are transferred in a timely and efficient manner.

David Wing, PhD, CBDT, CCRC (Research Staff): Dr. Wing has been involved in multiple studies of physical activity and function. Additionally, Dr. Wing serves as the Laboratory Director for the EPARC. In this capacity, he has developed expertise in the objective measurement of physical activity, fitness, function, sleep, and overall health utilizing a variety of accelerometers, heart rate monitors, and other biological sensors individually and in concert. Dr. Wing is primarily responsible for overseeing the implementation of the study protocol and will also assist in recruitment efforts. He will contribute to the preparation of manuscripts and dissemination of study results.

Daniel Moreno, MS (Research Staff): Mr. Moreno has an MS in Exercise Physiology and has more than 4 years of experience working in academic health research. He is a research associate in EPARC. He will be assisting in the implementation of the study protocol, including recruitment and screening efforts

Stephen Dozier (Research Staff): Mr. Dozier is a laboratory manager in Dr. Anthony Molina's lab at UCSD. He serves as the Managing Director of the UCSD Bioenergetics Core Facility. He will be responsible for conducting and overseeing the implementation of blood-based analyses including blood processing and assessment of mitochondrial function.

Jaclyn (Nikki) Bergstrom, MS: Ms. Bergstrom is a senior statistician in the Division of Geriatrics, Gerontology, and Palliative Care. She will manage the database and perform statistical analyses for the Multivitamin study.

TBN (Research Staff): BS or higher-level research associates with specific training in cell and tissue culture based assays and will assist in blood-based analyses.

10.1.5 SAFETY OVERSIGHT

The PI, Dr. Molina, will ensure that all study staff have appropriate certification and training to safely provide the measurements/assessments and intervention for this study. Dr. Han is responsible for medical safety. In this role, he provides oversight for the safety of the MVM intervention and the clinical assessments to be conducted.

10.1.6 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by the study coordinator.
- On-site review of gathered data and intervention compliance will occur at least 2x per month.
- Independent audits will not be conducted by individuals outside the study unless there are concerns from the IRB or other regulatory bodies.

10.1.7 DATA HANDLING AND RECORD KEEPING

10.1.7.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical study staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap, a 21 CFR Part 11-compliant data capture system provided by the University of California San Diego. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.7.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 2 years after the last participant has completed the final visit (V4). These documents will be retained for a longer period if required by local regulations. No records will be destroyed without the written consent of the PI. It is the responsibility of the PI to inform the study investigators when these documents no longer need to be retained.

10.1.8 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP). The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

The study PI and coordinator will use continuous vigilance to identify and report deviations within seven (7) working days of identification of the protocol deviation, or within seven (7) working days of the scheduled protocol-required activity. All deviations will be addressed in study source documents.

Protocol deviations will be sent to the reviewing Institutional Review Board (IRB) per their policies. The study coordinator will be responsible for knowing and adhering to the reviewing IRB requirements.

10.2 ADDITIONAL CONSIDERATIONS

10.3 ABBREVIATIONS

The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list).

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee

SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale

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