| | IRCM-2025-437 | Dec. 3, 2025 |
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**Title:** A Pilot Randomized Controlled Study of Combinatorial Gerotherapeutics for Healthspan Improvement

**Protocol Number:** ALRx011v3
**Version, Date:** v3, November 13, 2025

**Test Drug:** Rapamycin, Low-dose Naltrexone, Metformin, B12, NAD+, GSH, and the Infinite Supplement

**Indication:** Healthy, normative aging individuals between 60 years of age and 80 years of age seeking healthspan biomarker improvement

**Study Design:** Single-center, prospective, randomized controlled pilot study

**Study population:** AgelessRx Patients

**Site:** This is a decentralized trial. Participants can be located in any of the 50 states of the USA. All participation will be via telemedicine using the AgelessRx website (agelessrx.com) and services.

**Sponsor Name, Address, and Telephone Number:**

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**Institutional Review Board of the Institute of Regenerative and Cellular Medicine**

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**Compliance**: The study will be conducted in accordance with the standards of Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and all applicable federal and local regulations.

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**Confidential Information**



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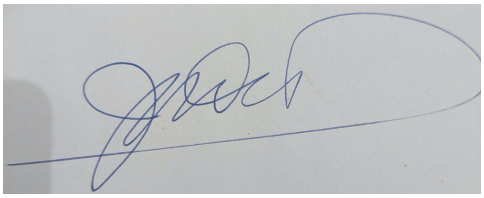
# 1 Signature Page

I have read this clinical protocol and confirm that to the best of my knowledge, it accurately describes the design and conduct of the study titled: A Pilot Randomized Controlled Study of Combinatorial Gerotherapeutics for Healthspan Improvement



Jenell Decker, MD Date: November 13, 2025

Stefanie Morgan, PhD Date: November 13, 2025

agelessrx

# 2 Synopsis

**Name of Sponsor/Company:** AgelessRx

**Name of product:** Rapamycin, Low-dose Naltrexone, Metformin, B12, NAD+, GSH, and Infinite supplement

**Title of study:** Pilot Study of the Efficacy of Combination Gerotherapeutics for Healthspan Improvement

**Objectives:**

Primary:

1. To evaluate the impact of different combinations of gerotherapeutics on measures of muscle, cognitive, and immune function.

Secondary:

1. To assess the impact of the combinatorial gerotherapeutics on sleep measures, perceived quality of life and longevity biomarkers.

**Methodology:**

This study is an interventional, randomized, controlled pilot trial exploring multi-modal gerotherapies and their impact on longevity-related outcomes.

Potential subjects will be recruited utilizing email and social media-based methods. They will be screened for eligibility and enrolled in the study upon obtaining informed consent.

In this proof-of-concept phase, a small sample size of 30 subjects (10 subjects in each arm) will be randomized into one of the three arms: 1) Control, 2) Multi-therapy (B12, Naltrexone, Metformin, and NAD+), or 4) Comprehensive Therapy (Rapamycin, Naltrexone, Metformin, B12, NAD+, GSH, and Infinite Supplement). The intervention period is 90 days. During the first 30 days, subjects will titrate up to maintenance dosing regimen of the assigned arm, which will be continued for the 60 days thereafter.

All groups will complete DXA scans, V02 Max tests, Creyos cognitive assessments, Edifice Health's iAge tests, iollo at-home blood testing kits, routine blood-work, and the following standardized survey questionnaires: ISQ, SF-36, RAPA, and SQS. Subjects will set-up Oura data-tracking for health biometric data with study staff assistance. Intervention group participants will also receive a guided meditation program and structured exercise program to follow throughout the study. In contrast, participants in the control group will engage in a standard exercise regimen (150 minutes per week) and listen to a neutral podcast designed to control for time and attention.

Participants will be evaluated at baseline and study end for measures of muscle function (by DXA scan of muscle mass and the VO2 max test to measure endurance capacity using a formal test and/or Oura ring estimate), cognitive function (by Creyos cognitive tests via web browser), immune function (by iAge and CD4+ : CD8+ ratio/lymphocyte : neutrophil ratio with Immune Status Questionnaire (ISQ) supplementation), SF-36 Quality of Life (SF-36 QoL) survey scores, PhenoAge (from blood biomarkers obtained from routine safety labs, detailed below), activity levels (RAPA questionnaire, Oura ring), metabolic health measures from routine and at-home blood tests, sleep improvements evaluated through Oura wearable device sleep quality and quantity as well as the Sleep Quality Survey (SQS), as well as other health indicators from Oura wearable data between baseline and study end. To ensure robustness of outcome measures, two measurements of each item 1 week apart will be used at baseline and again at study end for all measures except for DXA scan, V02 max formal test and Oura ring estimate, iAge and iollo kits, which will be used once at the beginning and once at the end of the study.

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| **Number of subjects planned:** 30 |
| **Diagnosis and main criteria for inclusion:** Adults 60-80 years of age who report a BMI of 26-30; SF36 score below the validated central tendency for 2 of: physical function, physical role limitations, energy, pain; final ISQ scores of <6; brain fog or difficulty with mental clarity; pre-diabetic; or who have a similar combination of reduced overall health functioning as determined by a physician. |
| **Statistical analysis:** Descriptive statistics for all variables, including outcome measures and adverse events, will be reported as mean and standard deviation (SD) for normal data or median and 25th-75th percentiles for potential non-normal data. Given the pilot nature of this round of testing, 95% confidence intervals, effect sizes, and minimum clinically important difference (MCID) will be utilized to provide a go/no go decision on further testing in lieu of formal (an underpowered) statistical hypothesis testing. Effect size and post-hoc power will then influence sample size calculations for subsequent rounds of testing. |

# 3 Table of Contents

# 4 List of Abbreviations

| Abbreviation | Definition |
|---|---|
| LDN | Low-dose Naltrexone |
| GSH | Glutathione |
| NAD+ | Nicotinamide Adenine Dinucleotide |
| LDR | Low-dose Rapamycin |
| B12 | B12 |
| SGLT2i | Sodium-glucose cotransporter-2 inhibitor |
| DXA | Dual-energy X-ray Absorptiometry (Bone Density Test) |
| SF-36 | Short Form Health Survey |
| ISQ | Immune Status Questionnaire |
| RAPA | Rapid Assessment of Physical Activity questionnaire |
| SQS | Sleep Quality Survey |
| GCP | Good Clinical Practice |
| AE | Adverse Event |
| SAE | Serious Adverse Event |
| ICF | Informed Consent Form |
| IRB | Institutional Review Board |
| PRO | Patient Reported Outcome |

# 5 Background and Rationale

## 5.1 Background on longevity research

Aging can be defined as a time-dependent functional decline in physiological function that may increase the vulnerability to diseases and eventually death. In 2013, a Cell publication defined nine hallmarks of aging (1). These hallmarks are genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication. Age-related diseases, such as cardiovascular diseases and cancer, are major causes of morbidity and mortality. Many treatments have been developed and are under development for each of these diseases. However, targeting the root cause of these diseases, aging, may decrease the incidence of these health issues and increase the quality-adjusted life years (QALY) of large groups of people.

## 5.2 Background on gerotherapeutic strategies

Biological aging is a gradual and heterogeneous process of systemic age-related decline. Unique organ-specific aging profiles dictate the pace of aging, from states of optimal health, to pre-disease, clinically diagnosed pathology, and ultimately death. A class of drugs, known as gerotherapeutics, are targeted at slowing organ aging by targeting the molecular mechanisms that underlie the process, giving rise to the hallmarks of aging. As many of these mechanisms are shared between organs, they often target multiple organs simultaneously and thus prevent multi-morbidity (2-4).

Historically, preclinical data has revolved around validating one gerotherapeutic candidate at a time to validate its effects on healthy longevity. However, emerging data from multiple labs, including the Intervention Testing Program (ITP), suggests that additive, and perhaps even synergistic, benefits may be achieved with combinatorial application of drugs having distinct age-related organ or mechanistic targets (5, 6). Similar to strategies that have been successfully utilized in effective cancer therapies and cardiovascular interventions, multi-therapeutic targeting of biological aging addresses key heterogeneous mechanisms and cellular dysfunctions that drive the diversity of age-related decline observed across individuals (7-10). While concerns have been raised that the increased potential for adverse side effects with this approach could undermine the therapeutic intent, it has not been well-studied to date.

Available evidence suggests that first generation gerotherapeutic interventions (e.g. FDA-repurposed drugs or naturally derived plant chemicals) used as monotherapies are largely insufficient to reverse aging substantially, particularly in multiple tissues (10, 11). Second generation gerotherapeutic modalities such as therapeutic plasma exchange and epigenetic reprogramming may overcome these challenges, but understanding of their use is limited to date, and they are not yet broadly accessible (12). However, it is plausible that strategic combinations of first generation gerotherapeutics may accomplish a similar outcome to second-generation modalities, but with more readily available and more completely understood medicines. Applying these in low doses to optimize safety profiles holds potential to define an early phase of next generation gerotherapeutics.

As such, we hypothesize that repurposing FDA-approved medications for gerotherapeutic applications in a combinatorial manner will target the unique aspects of cellular and organ aging biology that are sensitive to age-related decline in immune, neural, and musculoskeletal tissue to substantially reverse aging. We will test this with increasingly comprehensive combinations of gerotherapeutics (2, 4, and 7), to determine the minimum likely effective therapeutic set to improve measures of decline in three experimental study arms and a comparative control cohort. This pilot study will predominantly focus on ensuring these approaches are

reasonably safe, and that side effects of combination therapies do not present significant challenges to broader implementation for future, more comprehensive studies.

Our dual-intervention arm includes the most robustly supported gerotherapeutic in the preclinical space, low dose rapamycin (LDR), which has been widely suggested to reverse age-related decline of immune, cardiovascular, and oral health with self-reported improvements in physical functioning and age-related pain (13, 14). However, given the lack of evidence to suggest monotherapies are sufficiently effective in restoring multi-organ function across a heterogenously aging population, our dual-intervention arm also includes low dose naltrexone (LDN), which has shown broad clinical success for autoimmune and inflammatory conditions (15, 16). As evidence is mounting that aging can be broadly considered a process of gradually acquired autoimmunity affecting multi-organ function, these promising gerotherapeutics that primarily target mechanisms of immune aging form the core of our next generation gerotherapeutic strategy (17). Further, our combo and multi-therapeutic arm adds B12 to offer advanced support for a healthy nervous system. (18, 19). Finally, our comprehensive therapy arm additionally incorporates glutathione (GSH) and nicotinamide adenine dinucleotide (NAD+) supplementation to replenish critical endogenous molecules whose tissue-specific depletion is associated with accelerated aging phenotypes in multiple organ systems, and a proprietary supplement blend consisting of phytochemicals and metabolites with sufficient coverage to target and address all the hallmarks of aging, with the aim of increasing the probability of targeting the critical set of aging pathways that sufficiently address the heterogeneity of age-related decline in the target tissues (20-22).

## 5.4 Hypothesis and aims

We hypothesize that repurposing FDA-approved medications for gerotherapeutic applications in a combinatorial manner will target the unique aspects of cellular and organ aging biology that are sensitive to age-related decline in immune, neural, and musculoskeletal tissue to substantially reverse aging. We will investigate this through three aims:

**Aim 1: Determine whether LDR and LDN are sufficient to substantially improve healthspan measures of cognitive, muscle, and immune function.** We hypothesize that the combination of these two pro-longevity medications will improve healthspan measures broadly, however, whether they are sufficient to improve all of cognitive, muscle, and immune function, or just a subset of these, is unknown. To address this, we will evaluate these measures in participants taking LDR and LDN relative to controls.

**Aim 2: Identify whether a multi-therapeutic approach improves healthspan more than a comprehensive-therapeutic approach.** We hypothesize that targeting key elements of healthspan with a multi-therapeutic regimen will be more effective in improving healthspan outcomes than a comprehensive-therapeutic approach. We will thus evaluate healthspan measures of cognitive, muscle, and immune function in participants taking a multi-therapeutic intervention relative to comprehensive-therapy intervention.

**Aim 3: Establish whether a layered comprehensive therapy approach is necessary for substantial healthspan improvement.** We hypothesize that multi-faceted targeting of multiple areas of age-related declines with both therapeutic interventions and natural supplements will confer superlative healthspan benefits relative to other therapeutic approaches. Accordingly, we will test whether adding a proprietary natural supplement blend (Infinite), NAD+, and GSH to the multi-therapeutic approach outlined in Aim 2 measurably improves healthspan measure outcomes beyond the multi-therapeutic or comprehensive-therapy approaches.

We will predominantly focus on ensuring these approaches are reasonably safe, and that side effects of combination therapies do not present significant challenges to broader implementation

# 6 Objectives

## 6.1 Primary Objective

1. To evaluate the impact of different combinations of gerotherapeutics on measures of muscle, cognitive, and immune function.

## 6.2 Secondary Objective

1. To assess the impact of the combinatorial gerotherapeutics on sleep measures, perceived quality of life and longevity biomarkers.

# 7 Experimental plan

## 7.1 Study Design

Eligible participants will be randomly assigned to one of 3 study arms: multi-therapy, comprehensive therapy, or a control. In detail, the arms are:

- Arm 1 - Multi-Therapy: NAD+, LDN, B12, and metformin
    - In intervention month one, participants naive to all medications will be titrated on to low maintenance doses of each. NAD+ will be taken as a nasal spray of 30mg/day; LDN, will start at 1.5mg once daily and titrate up each week to 4.5mg daily; B12, take 1 cap per day (100mcg); Metformin will be taken 500mg daily. They will then remain on the maintenance doses of the combination therapy for the next 60 days.
- Arm 2 - Comprehensive Therapy: LDR, LDN, B12, metformin, NAD+, GSH, and Infinite
    - In intervention month one, participants naive to all medications will be titrated on to low maintenance doses of each. LDR will start at 2mg once per week and titrate up weekly to 6mg once per week; LDN, will start at 1.5mg once daily and titrate up each week to 4.5mg daily; B12, take 1 cap per day (100mcg); Metformin will be taken 500mg daily; NAD+ will be taken as a nasal spray of 30mg/day; GSH will be taken as a topical patch for 4 hrs, once per week; Infinite supplement will be taken once daily. They will then remain on the maintenance doses of the combination therapy for the next 60 days.
- Control: Placebo
    - In the control cohort, participants will take Vitamin C (1x/day) and Vitamin E (1x/week) as placebo agents.

In addition to medications, participants in the intervention groups will engage in a digital guided meditation program, while the control group will listen to a neutral podcast to account for time and attention. Participants in both intervention groups will also be asked to follow an exercise regimen for improved strength and muscle composition, while control participants will be asked to follow a general exercise program.

Participants will be evaluated at baseline and after 90 days on measures of muscle function (by DXA scan of muscle mass and VO2 max to measure endurance capacity), cognitive function (by Creyos cognitive tests via web browser), immune function (by iAge and CD4+ : CD8+ ratio/lymphocyte : neutrophil ratio with Immune Status Questionnaire (ISQ) supplementation), SF-36 Quality of Life (SF-36 QoL) survey scores, activity levels from a RAPA questionnaire and Oura ring data, PhenoAge (from blood biomarkers obtained from routine safety labs, detailed below), metabolic health measures from routine and at-home testing kits, and sleep improvements evaluated through Oura wearable device sleep quality and quantity as well as the Sleep Quality Survey (SQS). To ensure robustness of outcome measures, two measurements of each item 1 week apart will be used at baseline and again at study end for all measures except DXA/V02 max, iAge and iollo home testing kits, which will be used once at the beginning and once at the end of the study. Participants will be provided with an Oura ring to wear throughout their study participation. Data collected from the Oura ring will include general health metrics such as sleep, physical activity, heart rate, stress, and other relevant health indicators). One iollo kit will be given to each participant at study baseline and study conclusion to compare changes in metabolic biomarkers of health.

## 7.2 Cost of Participation

There are no expected costs to participate.

## 7.3 Estimated Study Duration

Duration: The total duration of the interventional study will be 90 days. An additional 2 months of participant recruitment and screening will take place beforehand, and 2 months of data analysis and interpretation will follow the conclusion of data acquisition in the interventional study. In total, this work is expected to require 7 months.

# 8 Subject Selection

## 8.1 Number of Subjects

We will include a total of 30 participants in the analysis. A complete dataset is defined as having a baseline score and subsequent response at least 90 days from baseline on all required weight, blood biomarker, and survey components of this study design.

## 8.2 Inclusion Criteria

- New, existing, or prospective AgelessRx patient
- Adults (60-80 years of age)
- Any sex
- Any ethnicity
- Willingness to provide informed consent and complete study assessments/procedures
- Willingness to attend virtual meeting check-ins/follow-ups
- Willingness and eligibility to take all medications used in this study
- Has at-risk indicators for decline on measures of cognitive, immune, and muscle function, as indicated by a combination of BMI of 26-30; SF36 score below the validated central tendency for 2 of: physical function, physical role limitations, energy, pain; final ISQ scores of <6; individuals that report brain fog or difficulty with mental clarity; pre-diabetic, or other comorbidities that result in reduced overall health functioning as determined by a physician

## 8.3 Exclusion Criteria

- Pregnant or breastfeeding individuals
- History of severe adverse reactions to study medications
- Significant psychiatric illness that may affect participation
- Determination of ineligibility for a study medication by AgelessRx medical team
- Concurrent participation in other conflicting clinical trials

## 8.4 Withdrawal

- Patients are free to withdraw from the study at any time.

# 9 Schedule of Assessments and Procedures

## 9.1 Patient Recruitment

Research participant recruitment for this interventional trial will be initiated through a general marketing campaign using email, social media, and similar outreach channels commonly employed for research recruitment by the AgelessRx team. Interested individuals will be directed to complete a screening questionnaire to assess their initial eligibility and to receive detailed information about the study, including the interventions, procedures, potential risks, information about the eligibility screening process, and the informed consent form. Participants will also be provided with a link to schedule a virtual meeting with the study coordinator to address any questions.

## 9.2 Screening

Patients interested in participating have been screened for eligibility criteria by AgelessRx medical staff via the telemedicine platform. The medical intake and consent built into the patient process will include inclusion/exclusion screening criteria and will serve as a screening tool for medical and research personnel. The consent language built into the patient intake workflow can be found in Appendix A.

## 9.3 Enrollment

Participants will be enrolled in the study for a total of 90 days. In the first 30 days, they will complete baseline testing and begin to titrate on to study medications. In the subsequent 60 days, they will continue on the new medication regimen (as determined by trial arm).

## 9.4 Evaluations

Primary outcomes assessed will be changes in muscle function (by DXA scan of muscle mass and VO2 max to measure endurance capacity), cognitive function (by Creyos cognitive testing), and immune function (by Edifice Health's iAge test and CD4+ : CD8+ ratio/lymphocyte : neutrophil ratio with Immune Status Questionnaire (ISQ) supplementation) from baseline to study end. To ensure robustness of outcome measures, two measurements of each item 1 week apart will be used at baseline and again at study end for all measures except DEXA/V02 max, iAge and iollo kits, which will be used once at the beginning and once at the end of the study.

Secondary outcomes assessed will be changes in measures of SF-36 Quality of Life (SF-36 QoL) survey scores, physical activity levels from a RAPA questionnaire and Oura ring data, PhenoAge (from blood biomarkers obtained from routine safety labs, detailed below), metabolic health measures from iollo testing kits, and sleep improvements evaluated through Oura wearable device sleep quality and quantity as well as the Sleep Quality Survey (SQS) between baseline and study end. Two measurements of SF-36 QoL, PhenoAge, and SQS will be conducted 1 week apart at baseline and study end to ensure robustness of outcome measures. Relevant health indicators such as sleep, physical activity, heart rate, stress, and VO2 max estimates will also be assessed using Oura wearable data. One iollo kit will be given to each participant at baseline and study end to compare changes in metabolic biomarkers of health.

## 9.5 Schedule of Events

### Schedule of Events

| Time Point (+/- 1 week) | Event | Arms 1-4 (Dual, Multi, Comprehensive Therapy and Control) |
|---|---|---|
| **Day 0 (Baseline)** | Baseline Assessments | Complete medical intake, medical history and demographics.<br>Begin intervention or placebo regimen as described for respective arms.<br>Complete DXA scan, VO2 max (formally administered test and estimated with Oura ring), Creyos, Edifice Health's iAge test, iollo, routine blood-work, ISQ, SF-36, RAPA, and SQS. Set-up Oura data-tracking with study staff assistance. |
| **Day 1-7** | Medication Titration: Week 1 | Multi-Therapy: LDN: 1.5mg/day, Metformin: 500mg daily, NAD+: 30mg/day (nasal spray), B12 1/day.<br>Comprehensive Therapy: As above + LDR 2mg/week, NAD+: 30mg/day (nasal spray), GSH: 4hr patch/week, Infinite: 1/day.<br>Placebo: Titration as per Multi-Therapy, but with placebo.<br>Control: Vitamin C 1x/day, Vitamin E once a week on same day |
| **Day 8-14** | Medication Titration: Week 2 | Multi-Therapy: LDN 1.5mg/day, Metformin: 500mg daily, NAD+: 30mg/day (nasal spray), B12 1/day.<br>Comprehensive Therapy: As above + LDR 4mg/week, NAD+: 30mg/day (nasal spray), GSH: 4hr patch/week, Infinite: 1/day.<br>Control: Vitamin C 1x/day, Vitamin E once a week on same day |
| **Day 15-21** | Medication Titration: Week 3 | Multi-Therapy: LDN 3mg/day, Metformin: 500mg daily, NAD+: 30mg/day (nasal spray), B12 1/day.<br>Comprehensive Therapy: As above + LDR 6mg/week, NAD+: 30mg/day (nasal spray), GSH: 4hr patch/week, Infinite: 1/day.<br>Control: Vitamin C 1x/day, Vitamin E once a week on same day |
| **Day 22-28** | Medication Titration: Week 4 | Multi-Therapy: LDN 4.5mg/day, Metformin: 500mg daily, Metformin: 500mg daily, NAD+: 30mg/day (nasal spray), B12 1/day.<br>Comprehensive Therapy: As above + continued NAD+, GSH, Infinite, LDR.<br>Control: Vitamin C 1x/day, Vitamin E once a week on same day |
| **Day 29-85** | Medication Maintenance: Week 5-12 | Multi-Therapy: Continue on LDN 4.5mg/day, Metformin: 500mg daily, Metformin: 500mg daily, NAD+: 30mg/day (nasal spray), B12 1/day.<br>Comprehensive Therapy: As above + continued NAD+, GSH, Infinite, LDR.<br>Control: Vitamin C 1x/day, Vitamin E once a week on same day |

| | | |
|---|---|---|
| **Day 85-90** | Final Assessments (90-Day Visit) | All groups: Complete DXA scan, VO2 max (formal test and with Oura ring), Creyos, Edifice Health's iAge test, iollo, routine blood-work, ISQ, SF-36, RAPA, SQS, final assessments, data collection and study exit procedures. |

# 10 Investigational Product

## 10.1 Investigational Drugs

Rapamycin: a well-known inhibitor of mTOR function, which promotes a cellular state of repair and improved cellular stress resistance characterized by enhanced autophagy, improved mitochondrial function, reduced chronic inflammation and enhanced adaptive immune function (23).

Low-dose Naltrexone: a synthetic non-selective opioid receptor antagonist, activates both the NRF-2 transcription factor to regulate anti-oxidant gene expression, cellular stress resilience, and anti-inflammatory effects, as well as toll-like receptor 4 (TLR4), to reduce aging-associated chronic inflammation (24); (25)

Metformin: lowers blood sugar levels primarily by blocking the production of glucose by gluconeogenesis. Metformin may also work by increasing the ability of skeletal muscle to remove glucose from the bloodstream and use it for energy. (26).

Methylcobalamin/vitamin B12: is generally referred to as the cobalamins, with cyanocobalamin as the most common form. Recent research has indicated that methylcobalamin provides an enhanced ability to support neurological function. Methylcobalamin helps maintain healthy glutamate activity in the brain, providing support for healthy brain cell activity. Methylcobalamin may also promote protein synthesis for healthy nerve cell maintenance. As a result, methylcobalamin has been shown to encourage healthy cognitive, memory, emotional, and nerve function. Methylcobalamin offers advanced support for a healthy nervous system (27).

NAD+: a critical coenzyme involved in over 500 metabolic reactions, essential for DNA repair, epigenetic maintenance, mitochondrial health, and regulating healthy immune function (28).

GSH: referred to as the master antioxidant with its primary function in managing oxidative stress and preventing free radical damage. Decreased GSH levels are associated with a wide range of age-related diseases, including neurodegenerative disorders (29)

Together, NAD+ and GSH are critical enhancing organ health and resilience in physiologically compromised populations, supplementation in elderly individuals is associated with salient improvements in cognitive and physical function within relatively short timeframes (30-33).

Infinite supplement: a proprietary blend of seven putative geroprotective compounds implicated in enhancing cellular function critical for managing cellular damage accumulation prevention of age-related decline (including Alpha ketoglutarate, Quercetin, Glucosamine, Carnosine, Pterostilbene,  Astaxanthin, and Curcumin) (34, 35)

## 10.2 Control Drug

Vitamins C and E will be utilized as control supplements for this experiment. Vitamin C is vital for building and repairing tissues, producing collagen, and supporting the immune system. Vitamin E is a fat-soluble antioxidant that protects cells from damage and supports immune function.

## 10.3 Dosing and Administration

### 11.3.1 Dose Escalation, Dose Adjustments, Stopping Rules

- Arm 1 - Multi-Therapy: LDN, B12, NAD+, and metformin
    - In intervention month one, participants naive to all medications will be titrated on to low maintenance doses of each. NAD+ will be taken as a nasal spray of 30mg/day; LDN, will start at 1.5mg once daily and titrate up each week to 4.5mg daily; B12 will be taken 1x daily; Metformin will be taken 500mg daily. They will then remain on the maintenance doses of the combination therapy for the next 60 days.
- Arm 2 - Comprehensive Therapy: LDR, LDN, B12, metformin, NAD+, GSH, and Infinite
    - In intervention month one, participants naive to all medications will be titrated on to low maintenance doses of each. LDR will start at 2mg once per week and titrate up weekly to 6mg once per week; LDN, will start at 1.5mg once daily and titrate up each week to 4.5mg daily; B12 will be taken 1x daily; Metformin will be taken 500mg daily; NAD+ will be taken as a nasal spray of 30mg/day; GSH will be taken as a topical patch for 4 hrs, once per week; Infinite supplement will be taken once daily. They will then remain on the maintenance doses of the combination therapy for the next 60 days.
- Control: Placebo
    - In the control cohort, participants are assigned to take Vitamin C 1x/day and Vitamin E 1x/week on the same day each week.

At the trial conclusion, participants may choose to continue with the medications by transferring care to AgelessRx, or titrating off of the medications. Those choosing to titrate off will be supervised by an AgelessRx physician until medications have all been safely discontinued.

### 11.3.2 Packaging and Labeling

Compounds will be dispensed by the following pharmacies according to state availability:

Everwell Specialty Pharmacies
6506 N Davis Hwy, Pensacola, FL 32504

Innovation Pharmaceuticals Inc.
301 Edgewater Pl Suite 100, Wakefield, MA 01880

Precision Pharmacy
2640 Merrick Road, Bellmore, NY, 11710

Valiant Compounding Pharmacy

1274 Anna J. Stepp Dr, Ypsilanti, MI 48197

Curexa
3007 Ocean Heights Ave, Egg Harbor Township, NJ 08234

Tailor Made Pharmacy
200 Moore Dr, Nicholasville, KY 40356

Fullscript
www.fullscript.com

Labeling and packaging will be handled by the entities listed above.

### 11.3.3 Storage

Tablets should be stored according to pharmacy instructions, provided on the container for each medication.

### 11.4 Concomitant Medications

If participants fit eligibility criteria but are on other medications, they should be continuing to take those at the prescribed dosages. They will be instructed to tell their other physicians, medical providers, and pharmacists of their enrollment in the trial. Any changes to concomitant medications or any planned surgery should be discussed with the PI immediately.

# 11 Adverse Event Reporting

## 11.1 Adverse Events Definitions

Adverse drug reaction (ADR): a noxious and unintended reaction to a drug at doses normally used in humans for prophylaxis, diagnosis, therapy of diseases, or for the modification of physiological function. A causal relationship is at least reasonably possible.

Adverse event (AE): an adverse occurrence experienced by a study subject during the course of the clinical trial that is not necessarily associated with the drug. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the investigational product, whether or not related to the investigational product. When an AE has been determined to be related to the investigational product, it is considered an adverse drug reaction.

## 11.2 Serious Adverse Events

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.

Adverse events will be graded according to the system below:

Grade 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; no intervention indicated (e.g. headache, nausea, abdominal discomfort)

Grade 2: Moderate; minimal, local or noninvasive intervention (e.g. vomiting, diarrhea, shortness of breath)

Grade 3: Severe; or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling (e.g. dehydration, hypotension)

Grade 4: Life-threatening ; urgent intervention indicated (e.g. respiratory failure, myocardial infarction, liver failure)

Grade 5: Death related to an AE

For adverse events (AEs) not included in the protocol defined grading system, 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".

All adverse events (AEs) must have their relationship to study intervention assessed by the research team clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

Related – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.

Not Related – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

## 11.3 Reporting of Adverse Events

### 11.3.1 Routine

The principal investigator will be notified about any adverse events. This information will be obtained through monitoring forms, emails, check-in surveys, and/or virtual visits.

The Principal Investigator and clinical trial staff will document this information in the participant's medical record. Participants will be asked to report any serious adverse event immediately to the Principal Investigator, this can be done by email or phone (after hours phone number available).

AEs will be documented using standard AE reporting (FDA regulations 21CFR314.80 and 21CFR213.32(s)). Both expected (already known) and unexpected AEs will be reported.

### 11.3.2 Expedited

Serious adverse events that occur while the research participant is actively participating in the research study will be reported to the IRB within 48 hours for the duration of the study (until study is closed at the IRB).

# 12 Statistical Analysis

Scores and responses from questionnaires will be compared across demographic information, history of use, reasons for use, etc., and analyzed in combination with biomarker and wearable data, as available. Descriptive statistics for all variables, including outcome measures and adverse events, will be reported as mean and standard deviation (SD) for normal data or median and 25th-75th percentiles for potential non-normal data. Given the pilot nature of this round of testing, 95% confidence intervals, effect sizes, and minimum clinically important difference (MCID) will be utilized to provide a go/no go decision on further testing in lieu of formal (an underpowered) statistical hypothesis testing. Effect size and post-hoc power will then influence sample size calculations for subsequent rounds of testing.

# 13 Ethics

## 13.1 Ethical Conduct of the Study

The study and any amendments will be reviewed by an Institutional Review Board (IRB). The study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki. The study will be conducted in accordance with good clinical practices (GCP).

## 13.2 Participant Information and Consent

Informed consent will be obtained for all subjects enrolled in the study. Participants will receive a digital PDF version of the informed consent documentation associated with the study (Appendix A). Participants will have the opportunity to ask questions before signing. Participants will respond to individual lines with Yes or No to indicate each section was read and understood, and then sign it electronically. A study coordinator will ensure the participants have completed the consent form and have agreed to understanding the study and implications of being a participant. It will be stressed that:

1) No benefits of any kind can be expected from participation in this trial
2) The subjects may withdraw from the trial at any time without a penalty of any kind
3) There may be risks associated with participating in the trial

Consent will be documented by a free text first and last name field confirming the participant understands the study. Identity will be validated by way of state-issued ID upload alongside an image of the participant. All participants will be provided a PDF version of the consent form for their reference and storage.

## 13.3 Study Participant Confidentiality

All study records for analysis will be de-identified, so that records cannot be directly linked to the participant and are only linked to the participant via coded identifiers. Data will be stored on a password-protected HIPAA-compliant cloud service.

# 14 Administrative Procedures

## 14.1 Modifications to the Protocol

Modifications to the protocol will be added to the Clinical Study Protocol and communicated with the IRB.

## 14.2 Plans for Dissemination of Findings

We intend to disseminate the findings primarily in five ways:

1) Publications in peer-reviewed medical journals
2) Lectures at scientific conferences
3) Lectures at non-scientific public events
4) Announcements via the AgelessRx website
5) Outreach to various media outlets

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# Informed Consent Form

## Consent to Participate in a Research Study

**Study Title:** A Pilot Randomized Controlled Study of Combinatorial Gerotherapeutics for Healthspan Improvement

**Sponsor:** AgelessRx, Inc.
Address: 2370 E Stadium Blvd #2049 Ann Arbor, MI 48104
Tel: 650-503-9990
Fax: 650-729-0869
Email: info@agelessrx.com

**Principal Investigators:**

Jenell Decker, MD
Address: 2370 E Stadium Blvd #2049, Ann Arbor, MI 48104
Phone: (650) 503-1889
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Stefanie Morgan, PhD
Address: 2370 E Stadium Blvd #2049 Ann Arbor, MI 48104
Tel: 413-563-9686
Email: stefanie@agelessrx.com

**Site:** This is a decentralized trial. Participants can be located in any of the 50 states of the USA. All participation will be via telemedicine using the AgelessRx website (agelessrx.com) and services.

## Key Information

### What should I know about a research study?

- You can choose whether or not to take part.
- You can agree to take part and then later change your mind.
- Your decision whether or not to participate will not be held against you.
- You can ask all the questions you want before you decide.

### What is the purpose, procedures and duration of this study?

We invite you to take part in a research study because you have shown interest in improving at-risk healthspan indicators for decline on measures of cognitive, immune, and muscle function or reduced overall health functioning as determined by a physician. The purpose of this study is to evaluate combinations of known gerotherapeutics to identify a minimum regimen that substantially improves cognitive, muscle, and immune functions. These combinational modalities are investigational (experimental). The interventions are approved by the Food and Drug Administration (FDA) separately; however, they are not approved as combinatorial modalities which this study aims to explore.

You will be assigned to one of the interventional or control arms for 90 days. Once assigned, you will follow a titration (increase per week) regimen for that arm, instructed by the research team, for the first 30 days. After the first 30 days, you will remain with a steady regimen for 60 days thereafter. You will be asked to complete questionnaires, cognitive testing, blood samples, a digital guided meditation program, exercise program, DXA body imaging scans and VO2 max tests. You will also be asked to provide Oura ring wearable health data to track healthspan measures.

Your participation in the research will last about 90 days.

**Why might you choose not to participate in this research study?**

The study may involve risks, including but not limited to gastrointestinal discomfort, changes in mood, and other side effects associated with the alternative therapies. See Risks for more details.

**What are my other choices if I do not take part in this study?**

The alternative to being in this study is to not take part.

**Do the researchers or institution have any conflicts of interest relating to this study?**

One or more of the Investigators conducting this study serve as consultants or employees for the company that makes products used in this study. These financial interests are within permissible limits established by the local institutional Conflict of Interest Policy. If you have any questions regarding conflicts of interest, please ask your study doctor.

## Detailed Information

**How Many People Will Take Part in this Study?**

Approximately 30 people will take part in this study.

**What is involved if you decide to take part in this research study?**

Study Terms:

- Randomization: a process will be used to assign you, by chance, to one of the study groups. Neither you nor your doctor can choose which group you are in.
- Low-dose Rapamycin (LDR): This is a treatment using a very small amount of rapamycin, a drug that helps slow down the aging process by blocking certain pathways in the body that contribute to inflammation and cell damage. LDR may improve health, extend lifespan, and support tissue repair.
- Low-dose Naltrexone (LDN): This involves taking a small dose of naltrexone, a drug that normally treats addiction. At low doses, it may help boost the immune system, reduce inflammation, and relieve symptoms of autoimmune diseases, chronic pain, and other conditions.
- B12: Recent research has indicated that methylcobalamin provides an enhanced ability to support neurological function. Methylcobalamin helps maintain healthy glutamate activity in the brain, providing support for healthy brain cell activity. Methylcobalamin may also promote protein synthesis for healthy nerve cell maintenance. As a result, methylcobalamin has been shown to encourage healthy cognitive, memory, emotional, and nerve function. Methylcobalamin offers advanced support for a healthy nervous system..
- Metformin: Metformin is a medication used to help people with type 2 diabetes to manage their blood sugar levels. Metformin lowers blood sugar levels primarily by blocking the production of glucose by the liver, a process called gluconeogenesis. Metformin may also work by increasing the ability of skeletal muscle to remove glucose from the bloodstream and use it for energy.
- Nicotinamide Adenine Dinucleotide (NAD+): NAD+ is a molecule found in every cell that plays a key

role in energy production, DNA repair, and maintaining healthy brain function. Increasing NAD+ levels, often through supplements or other interventions, may help slow aging, improve energy, and promote overall health.
- Glutathione (GSH): Glutathione is an antioxidant that helps protect cells from oxidative stress and damage. It also plays a key role in detoxifying the body, supporting the immune system, and reducing inflammation. Boosting glutathione levels is often used for improving overall health and longevity.
- Infinite Premium Longevity Support: a nutraceutical formulation designed to enhance cellular health and mitigate age-related physiological decline. The ingredients include Calcium Alpha-Ketoglutarate, Quercetin, Glucosamine, Carnosine, Pterostilbene, Astaxanthin, and Curcumin.
- Placebo/control: Vitamin C and Vitamin E supplements

Interventions:

You will be randomized into one of the following arms:

- Arm 1 Multi-Therapy: B12, LDN, NAD+, and Metformin
- Arm 2 - Comprehensive Therapy: LDR, LDN, B12, Metformin, NAD+, GSH, and Infinite Premium Longevity Support
- Control: Vitamin C and E supplements

Specimen Collection:

- Commercially-available mail-based kits for advanced longevity biomarkers (Edifice Health's iAge test and iollo) will be completed at-home and returned by mail. The study staff will be available for assistance.
- Bloodwork will be completed for all participants at the Quest Diagnostics or LabCorp facility nearest to them (identified with the assistance of study staff).

Questionnaires/Assessments:

- Immune Status Questionnaire (ISQ)
- SF-36 Quality of Life (SF-36 QoL)
- Rapid Assessment of Physical Activity (RAPA) questionnaire
- Sleep Quality Survey (SQS)
- Creyos Cognitive Testing

Imaging and Testing:

- DXA Scans

- VO2 Max tests (formal test administered at a facility and with Oura ring estimate)

Wearables:

- Oura Ring (to measure general health indicators such as sleep, physical activity, heart rate, etc.)

Additional:
- A digital guided meditation program
- A guided at-home exercise program

## Risks

**What are the risks of participating in the research study?**

- Interventions: The potential risks of these interventions vary but may include common side effects like nausea, headaches, and digestive issues. Some, like low-dose rapamycin can increase the risk of infections or cause skin discoloration and dizziness. Others, such as metformin, may lead to GI discomfort, such as stomach cramps, diarrhea, nausea, bloating or constipation. Glutathione and NAD+ supplements can cause mild discomfort like bloating or fatigue. In some cases, these treatments may interact with other medications or have more serious effects. These risks have been deemed minimal and will be monitored closely by the research team. You will be instructed to notify the research team of side-effects and adverse events.
- Blood draw: The insertion of the needle to draw blood can be painful; however, the discomfort is brief. For most people, needle punctures to get blood samples do not cause any serious problems; however, they may cause bleeding, bruising, discomfort, infections, dizziness, or fainting.
- Questionnaire/Survey Research: Some of the questions we will ask you as part of this study may make you feel uncomfortable. You may refuse to answer any of the questions and you may take a break at any time during the study. You may stop your participation in this study at any time.
- Unknown Risks: There may be risks or side effects related to the study interventions that are unknown at this time. You will be notified of any significant new findings that become known that may affect your willingness to continue in the study.

**How will my data/specimens be used?**

Your data/samples/images may be sent outside of the AgelessRx for research purposes only. We will allow data access, use, and material transfers to XPRIZE as needed for judging and future analyses. Any personal information that could identify you will be removed before they are shared.

Collection of biospecimens by third-party testing vendors will be treated in accordance with the procedures set up by vendors for maintaining and storing samples and sample data. While no genetic information is intended to be collected in this study, best efforts will be made to minimize exposure of any associated PHI and identifying biological information in perpetuity. A sample containing the participant's DNA may be archived and it could be analyzed by Whole Genome Sequencing, so the participant's DNA gene sequence may be known.

Additional information on the specific sample handling practices of each third-party vendor used for testing in this study is available upon request from the AgelessRx research staff.

**Confidentiality Risks**

There is a small, but non-zero potential risk of loss of confidentiality of your data. Every effort will be made to keep your information confidential as it will be stored in a secure database and only accessible to the research study team. Personal information will be closely protected, and you will not be identifiable in any publication resulting from this study.

Your medical information is unique to you. There is a small, but non-zero risk that someone outside of the research study could get access to your study records or trace information in a database back to you. While the chance that someone could access and misuse your information is believed to currently be very small, it is possible that the risk may increase in the future as people find new ways to access information.

**What are possible benefits of participating in the research?**

Participation in this study may help to improve your healthspan and longevity, but it is also possible that your health may worsen. There is no guarantee that you will personally benefit by participating in this research study. Your participation in this study may provide information that may help others improve their healthspan and lifespan in the future.

**Are there any costs to you if you participate in this study?**

There is no cost to you to be in this research study.

**Authorization to Use/Disclose Protected Health Information**

Study results may be shared in medical journals, at scientific meetings, and in other mediums without your identifying information. Your records will be confidential and your identity will not be shared in medical journals, at scientific meetings, and in other mediums without your express consent.

AgelessRx has rules and procedures to protect information about you. Federal and State laws also protect your privacy. The research team working on the study will collect information about you. This includes your health information, data collected for this research study and personal identifying information including your name, address, date of birth and other identifying information.

Generally, only people on the research team will know your identity and that you are in the research study. However, sometimes other people at AgelessRx may have access to your information on a need-to-know basis. These include people who review research studies including the Institutional Review Board and Research Compliance, their staff, lawyers, or other AgelessRx staff.

People outside AgelessRx may see your information for this study. Examples include government groups (such as the Food and Drug Administration), safety monitors, other hospitals in the study and the sponsor of the research and their agents. AgelessRx will do our best to ensure your information is kept confidential and that only the health information which is minimally required to conduct the study is used or disclosed to people outside AgelessRx.

You do not have to give this permission to use and give out your information; however you will not be able to participate in this research study without providing this permission by signing this consent form. The use and disclosure of your information has no expiration date.

You may cancel your permission to use and disclose your information at any time in writing. If you do cancel your permission to use and disclose your information, your participation in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in the study.

**Clinical Trials Language**

A description of this clinical trial will be available on http://www.ClinicalTrials.gov. This Website will not include information that can identify you. At most, the Website will include a summary of the results. You can search the Website at any time.

**Who do you call if you have any questions or problems?**

If you have any questions or concerns about the research, or develop a research-related problem, you should contact the research team directly at research@agelessrx.com or (650) 503-1889, press 1 to leave a voicemail. If you have questions about your rights as a research participant, you should contact the Institutional Review Board.

**What are your rights as a research participant?**

Taking part in this study is voluntary. You will be told of any new, relevant information from the research that may affect your health, welfare, or willingness to continue in this study. You may choose not to take part or may leave the study at any time. Withdrawing from the study will not result in any penalty or loss of benefits to

which you are entitled. If you decide to withdraw from the study you should discuss with your study doctor your decision to ensure a safe withdrawal.

If you leave the study early, AgelessRx may use your health information that has already been collected in accordance with the processes outlined above if the information is needed for this study or any follow-up activities.

## Signatures

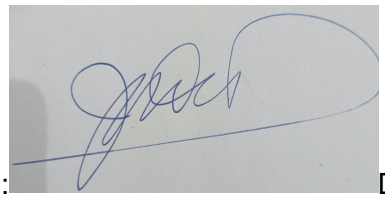
**Statement of Participant**

I have read and have had verbally explained to me the above information and have had all my questions answered to my satisfaction. I understand that my participation is voluntary and that I may stop my participation in the study at any time. I understand that a copy of this consent will be provided to me.

Should I wish to contact an impartial third party not associated with this study, I may contact James P. Faber, secretary of the Institutional Review Board (IRB) of the Institute of Regenerative and Cellular Medicine (IRCM), which reviewed this study for ethical compliance: jpfaber@ircm.org or (786) 271-2156.

By signing below, I confirm that I have read and understood the information provided, have had the opportunity to ask questions, and agree to participate in this study.

Participant Signature: _____ Date: _____

Principal Investigator Signature:  Date: __11/13/2025_____