Appendix AA.

Senolytics to Alleviate Mobility Issues and Neurological Impairment in Aging "STAMINA"

Study Protocol

IRB Pro00053594
ClinicalTrials.gov identifier: NCT ######

CHAPTER 1: INTRODUCTION

Abnormalities in cognition and mobility are common accompaniments of aging that often precede the development of Alzheimer's disease. Among their many etiologies, these abnormalities are associated with alterations in the regulation of cerebral blood flow to frontal regions of the brain that subserve executive functions and gait speed. We have previously shown that treatment with cocoa flavanols can improve blood flow in response to a cognitive task (neurovascular coupling [NVC]), as well as executive function in older people with impaired NVC. These compounds can also reduce the number of senescent cells and their toxic secretory products (SASP) in a variety of tissues.

In mice, "senolytic" compounds such as flavanols and tyrosine kinase inhibitors, have been shown to reduce neurofibrillary tangle density, neuron loss, and ventricular enlargement, and in humans with idiopathic pulmonary fibrosis, improve gait speed and other functional abilities. Based on these findings, we hypothesize that the flavanol, Quercetin, and tyrosine kinase inhibitor, Dasatinib, (D+Q) will improve NVC in response to an executive task, reduce circulating SASP components, and in so doing, improve cognition and mobility in older adults who are at risk of Alzheimer's disease.

Our long-term goal of this study is to prevent common age-related impairments in cognition and mobility that lead to the development of Alzheimer's disease by interrupting one of the fundamental mechanisms of aging, namely the accumulation of senescent cells and their damaging products. As a first step, this study will determine the feasibility and safety of administering Quercetin and Dasatinib to eliminate these cells from the body, and test whether their elimination can improve brain blood flow, cognition, and mobility in older adults at risk of developing Alzheimer's disease.

The overall aim of this study is to demonstrate the feasibility and safety of administering intermittent doses of Dasatinib and Quercetin in older adults at risk of Alzheimer's disease. We will conduct a 12-week single arm, open label, pre-post pilot study in 12 older adults aged ≥65 years with slow gait speed (<1.0 m/sec) and Mild Cognitive Impairment (MCI, defined as a Telephone Montreal Cognitive Assessment Score (tMoCA) <19 points). Participants will be asked to take 100 mg of Dasatinib and 1,250 mg of Quercetin for 2 consecutive days, every two weeks over a period of 12 weeks (i.e., 12 doses in total). During this study we will evaluate measures of feasibility, safety, physical function and cognitive function. Our overall hypothesis is that co-administration of Dasatinib and Quercetin in older adults will be feasible and safe, without serious adverse effects.

Innovation and Impact: The results from this study will obtain preliminary evidence on the feasibility of a novel approach that may improve cerebral blood flow regulation, mobility, and cognition in older adults, and prevent their progression to Alzheimer's disease. The study may also help establish proof-of-concept that the cognitive and functional disabilities of older age arise, in part, from the secretory products of senescent cells and can be alleviated by senolytic agents.

CHAPTER 2: BACKGROUND

Abnormalities in cognition and mobility are common accompaniments of aging and predictors for the development of Alzheimer's disease.[1-3] They are associated with vascular risk factors and microvascular damage to critical neural circuits in the brain, [4-6] especially those in periventricular and frontal lobe regions nourished by the middle cerebral artery (MCA). We have previously identified abnormalities in cerebral blood flow regulation in this territory that are associated with slow gait, falls, and cognitive dysfunction.[7,8] We also demonstrated improvements in MCA cerebral blood flow with 1 and 2 weeks of treatment with flavanol-rich cocoa.[9] Our group showed that 4 weeks' consumption of cocoa flavanols can improve blood flow in response to a cognitive task (neurovascular coupling, NVC), as well as Trail Making Test scores in older adults with impaired NVC.[10] Other investigators have shown that cocoa flavanols can improve Trail Making and Verbal Fluency in older people with mild cognitive impairment [11] (MCI). Flavanols can interrupt amyloidogenic processes, prevent tau phosphorylation, inhibit the development of Alzheimer's disease, and reverse cognitive deficits in rodents.[12] Therefore, they have been touted as possible therapeutic agents to prevent the development or progression of Alzheimer's disease.[12-14] However, to our knowledge, flavanols have not been rigorously studied for their effect on cognition and mobility in humans at risk of Alzheimer's disease.

The accumulation of senescent cells and their products, which are components of the senescence-associated secretory phenotype (SASP), are associated with age-related deficits in cognition and mobility, including Alzheimer's Disease.[15] In mice and humans, "senolytic" compounds such as the plant-derived flavanols and tyrosine kinase inhibitors can reduce the number of senescent cells in a variety of tissues.[15,16] They have also been shown to reduce neurofibrillary tangle density, neuron loss, and ventricular enlargement.[17,18] Senolytics improve carotid vascular reactivity and exercise capacity; delay, prevent, or alleviate a range of age-related disorders and chronic diseases; enhance health span, decrease frailty, and increase survival.[15,16,19-21] Moreover, these compounds have been found to be safe and well-tolerated in humans.[22] Many of these biologic effects, including the improvement in cerebral blood flow regulation that we previously observed, could improve gait and cognition, declines in which are both predecessors of Alzheimer's disease. To date there are no randomized controlled trials (RCT) examining these important outcomes.

Based on our previous work with cocoa flavanols, and that of our collaborators Dr. James Kirkland and colleagues at Mayo Clinic with other senolytics, we hypothesize that the joint administration of the flavanol, Quercetin, and tyrosine kinase inhibitor, Dasatinib, (D+Q) will be feasible and safe. Prior studies suggest that D+Q is an excellent candidate for intervention, but human data supporting its testing in older adults with mobility impairment or MCI are lacking. This study will provide preliminary evidence on mobility and cognitive measures to design future studies with the ultimate goal of improving cerebral blood flow to watershed regions of the brain that subserve executive functions and gait speed, and reducing circulating SASP components, thereby improving cognition and mobility. The pilot project described in this application will develop these data, and will provide the experience necessary to design an RCT measuring the effects of these two compounds on gait and cognition in larger numbers of older adults.

Together, these discoveries will enable us to appropriately design future, large-scale efficacy trials to determine if D+Q has potential to alleviate age-related impairments in cognition and mobility in older adults at risk of Alzheimer's disease.

CHAPTER 3: RESEARCH DESIGN AND METHODS

3.1 Study Objectives

The overall aim of this study is to demonstrate the feasibility and safety of administering intermittent doses of Dasatinib and Quercetin in older adults at risk of Alzheimer's disease. We will conduct a 12-week single arm, open label, pre-post pilot study in 12 older adults aged ≥65 years with slow gait speed (<1.0 m/sec) and Mild Cognitive Impairment. Participants will be asked to take 100 mg of Dasatinib and 1,250 mg of Quercetin for 2 consecutive days, every two weeks over a period of 12 weeks (i.e., 12 doses in total). During this study we will evaluate measures of feasibility, safety, physical function, and cognitive function. Our specific aims are:

1) Determine the feasibility, safety, and recruitment challenges of studying intermittent doses of Quercetin and Dasatinib (D+Q) in older adults at risk of Alzheimer's disease. We will evaluate the number of volunteers needed to be screened to identify eligible participants, the number of protocol deviations that are necessary to ensure safe and scientifically rigorous human subject participation (reported to the FDA and IRB), the frequency of any adverse drug effects, and compliance with medication administration.

2) To obtain preliminary data on the effect of this D+Q regimen on: a) sitting and standing cerebral blood flow (CBF), and neurovascular coupling (NVC) during an executive task, b) gait speed, c) and executive function. We will measure CBF during sitting and standing, NVC during an N-Back cognitive task, 4 meter gait speed, and executive function via the Trail Making Test (TMT) pre- and post-intervention to estimate the average changes and variability of these measures. Such information will be used to design future, large-scale efficacy trials.

3) To develop preliminary evidence concerning whether D+Q is associated with a) a reduction in biomarkers of senescence in serum and urine and senescent cells in blood, and b) whether reductions in these biomarkers are associated with improvements in NVC, gait speed, and executive function. We will measure biomarkers of senescence in urine and plasma and senescent cells in blood pre- and post-intervention to obtain preliminary evidence of potential mechanisms.

Our overall hypothesis is that a 12 week co-administration of intermittent doses of Dasatinib and Quercetin in older adults at risk of Alzheimer's disease will be feasible and safe.

3.2 Overview

We will conduct a single-site, single-arm, open label pilot study of D+Q in older adults at risk of Alzheimer's disease. Screened and eligible participants will perform baseline physical and cognitive assessments, as well as provide a blood and urine sample. They will then be asked to take 100 mg of Dasatinib and 1,250 mg of Quercetin for two consecutive days. Every two weeks, the same cycle will be repeated where participants are asked to take the same dose of study medications for 2 consecutive days. A total of six, 2-day administrations of study medications will take place over a total of 12 weeks. Two weeks after their last dose, participants will complete a follow-up assessment of physical and cognitive function, as well as provide a blood and urine sample. Safety and possible adverse events will be monitored throughout the entire duration of the study as described below.

3.3 Organizational Structure of the Team

The trial will be conducted under the leadership of Dr. Lewis A. Lipsitz, Principal Investigator, and administered at the Hebrew Rehabilitation Center (HRC). Dr. Lipsitz will be responsible for leadership of all aspects of the design, conduct, analysis and interpretation, and reporting of this pilot study.

The trial's Steering Committee will include Dr. Lipsitz and co-Investigators Drs. Thomas Travison (clinical trialist and biostatistician) and Courtney Millar (postdoctoral fellow). Additionally, our collaborators Drs. James Kirkland and Tamar Tchkonia at the Mayo Clinic, who will be measuring biomarkers of senescence, will serve as members of the Steering Committee.

The Steering Committee will meet at least monthly, or more frequently as needed. Functions of the Committee will include monitoring the progress of the trial, overseeing the scientific direction of the study, assuring quality

control of data collection and statistical analyses, reviewing scientific and safety reports from the study, and approving publications and presentations of study results.

The trial's Oversight/Operations Committee will be the day-to-day working group of the study, and will include Drs. Lipsitz, Travison, and Millar; the project directors, Margaret Gagnon, RN, and Ikechukwu Iloputaife; and research associate and/or other study staff. The Oversight Committee will meet weekly or more as needed to monitor ongoing study progress, review safety data, resolve problems, and plan for the next stages of the trial.

3.4 Overall Timeline

Months	3	6	9	12	15	18	21	24
Start-up	X							
Recruit, Treat & Assess Subjects		X	X	X	X	X		
Operations Committee Weekly Meetings	X	X	X	X	X	X	X	X
Steering Committee Monthly Meetings	X	X	X	X	X	X	X	X
DSMB Meetings		X		X		X		
Biomarker Assays						X	X	
Data Analysis							X	X
Final Publication								X

We propose a 2-year timeline for this pilot study, with a 3-month startup period, 15 month clinical intervention, and 6 month final period for biomarker assays, analyses, and publication.

The first 3 months will be dedicated to study start up activities and the study infrastructure will be developed. During this time, the IND and IRB applications will be submitted, the Clinical Trials.gov application will be completed, and the Safety Monitoring Board members will be determined and convened to review and approve the final intervention, data gathering, and safety monitoring protocols. Study staff will be trained during all-team Study Initiation Visits.

Following study start-up, recruitment and enrollment activities will begin and are anticipated to be completed by month 18. The study intervention, subject assessments, and data processing will proceed simultaneously.

Biomarker analyses and data cleaning and analysis will begin in month 18 and will be completed by month 24, with the preparation of a final study report for publication.

The Operations study team will meet weekly throughout the study to review and record the study progress and human subject safety. The Steering Committee will meet monthly throughout the study. The DSMB will meet every 6 months.

3.4 Inclusion/Exclusion Criteria

Individuals expressing an interest in participating after recruitment out-reach will be screened over the telephone. Those eligible and interested will be scheduled for the in-person screening visit (Visit 1).

Participants will complete several in-person screening procedures at Visit 1 to confirm that they meet the following inclusion criteria.

Inclusion Criteria

- Men and women ≥65 years
- Ambulatory
- Community-dwelling

- Slow gait speed (<1 m/sec)
- Mild Cognitive Impairment (Telephone MoCA score <19 points, which is indicative of cognitive impairment[23])

Exclusion criteria have been selected to ensure safety and optimize compliance, while minimizing confounds due to overt disease or conditions that may significantly influence study outcomes. Exclusions may be identified during the initial telephone screening, or during the in-person screening as described below.

Pre-screen Telephone Exclusion Criteria - Potential participants will be assessed over the phone for the following:

- Age <65 years
- Telephone MoCA score < 10 points, which corresponds to a full MoCA score of 14 points[24] and indicates dementia[25]
- Unwilling to take study medications or follow study protocol
- Non-ambulatory
- Inability to independently perform Katz Activities of Daily Living (ADLs)[26]
- Allergies to Quercetin and/or Dasatinib
- Hospitalization within 6 months
- Unstable coronary artery disease (myocardial infarction within 6 months or angina), stroke or transient ischemic attack in the past 6 months, chronic heart failure, current or chronic history of liver disease, neurodegenerative disease including Parkinson's Disease, anemia, or chronic renal disease, or drug or alcohol abuse in the previous 5 years

In-person Screening Exclusion Criteria - Potential participants will be assessed in-person for the following (See Appendix A for clinical safety exclusion thresholds/definitions):

- Those allergies to Quercetin and/or Dasatinib
- Unstable coronary artery disease (myocardial infarction within 6 months or angina), or as per clinical judgement
- Hospitalization within 6 months, or as per clinical judgement
- Stroke or transient ischemic attack in the past 6 months, or as per clinical judgement
- Chronic heart failure, or as per clinical judgement
- Current or chronic history of liver disease, neurodegenerative disease including Parkinson's Disease, or as per clinical judgement
- Drug or alcohol abuse in the previous 5 years, or as per clinical judgement
- QTc prolongation (>450 ms), or as per clinical judgement
- Anemia (Hgb<9), or as per clinical judgement
- Thrombocyopenia (Platelets <150 x 10^3/mcL), or as per clinical judgement
- Neutropenia (Absolute Neutrophil Count ,<1,500 cells/mcL), or as per clinical judgement
- Prolongation of prothrombin time (>13 seconds) or International Normalized Ratio (>1.1), or as per clinical judgement
- Indications of current fluid retention, including pulmonary rales or >+1 ankle edema, or as per clinical judgement
- History or current diagnosis of pulmonary hypertension by self-report, previous echocardiogram, right ventricular or right atrial enlargement or strain on EKG, examination findings of right-sided heart failure (JVD, HJR, peripheral edema), or as per clinical judgement.
- Chronic renal disease (Glomerular Filtration Rate [GFR< 30 mL/min/1.73 m^2]), or as per clinical judgement
- Chronic use of the following medications: anti-arrhythmic medications, antipsychotics and anxiolytics, anti-platelet or anti-coagulant medications other than aspirin, quinolone antibiotics, or drugs metabolized by the same liver enzymes as Quercetin or Dasatinib (See Appendix B for a complete list of contraindications, cautions, and interactions of study medications).

- If we are unable to insonate the middle cerebral artery through a temporal bone window on at least one side using transcranial Doppler ultrasound (TCD)

3.5 Number of Subjects and Study Duration

We will recruit a total of 12 individuals (both men and women), in proportion to the gender and racial distribution of the greater Boston population, through local newspaper and internet advertisements, physician referrals, our registry of research volunteers, Hebrew SeniorLife (HSL) senior housing sites, and patient registries at Beth Israel Deaconess Medical Center and the Harvard CTSA. Participants will remain in the study for a total of 14 weeks.

3.6 Study Endpoints

Primary Study Endpoints
The primary feasibility and safety outcomes for Aim 1 will be:

1. The number of volunteers needed to be screened to identify eligible participants
2. The number of protocol deviations necessary to enable subjects to participate comfortably and safely while maintaining scientific rigor (reported to the FDA and IRB)
3. The frequency of any adverse drug effects
4. Compliance with medication administration

For Aims 2 and 3, the primary outcome variables will be:

1. Cerebral blood flow (CBF) during an N-Back cognitive task (NVC)
2. Executive function (Trails B minus A score; TMT)
3. The 4 meter gait speed

Secondary Study Endpoints
The secondary outcomes for this study will be:

1. The Short Physical Performance Battery score (SPPB)[27]
2. The Timed Up and Go (TUG) test[28]
3. Grip strength
4. Slowing of gait speed during a subtraction task (dual task cost),[29]
5. Circulating and urinary inflammatory markers, senescent cells, and SASP factors.[22]

3.7 Study Medications

Each participant will be given a planned maximum daily dosage of 1,250 mg of Quercetin (the contents of five 250 mg capsules) and 100 mg of Dasatinib orally once a day for 2 days (one will be taken at the study clinic, one will be taken at home), every 2 weeks for 6 cycles, over 12 consecutive weeks. Our proposed dose was determined based on the dose provided in the first reported clinical trial of D+Q. In patients aged 55-84 years with Idiopathic Pulmonary Fibrosis - a fatal, relentlessly progressive, cellular senescence-related disease - a 3 week course of intermittent D+Q (9 doses) was found to be safe and well-tolerated by the subjects in that clinical trial, and enhanced physical function within a month of initiating treatment.[22] Furthermore, there were no changes in body weight, vital signs, or clinical chemistries following the intervention.[22] Only one serious adverse event was reported following completion of the intervention. This was a possible bacterial multifocal pneumonia and pulmonary edema superimposed on IPF, which resulted in temporary hospitalization with subsequent complete resolution. Since our subjects will not have underlying pulmonary disease, this is highly unlikely to occur.

CHAPTER 4: RECRUITMENT AND DATA COLLECTION

4.1 Recruitment Overview and Target Population

Participants will be recruited from the Boston area community, senior housing facilities in urban and suburban areas, and research recruitment repositories. We will utilize a multi-pronged approach to meet our recruitment goals:

- We will recruit from the research repository that resides at HRC, which currently contains approximately 200 individuals with known demographics and health history who were screened with cognitive and gait assessments for previous research studies within our laboratory and have expressed interest in future research participation.
- We will perform medical record reviews to identify potentially eligible individuals at the Hebrew SeniorLife (HSL) geriatric medicine practices.
- We will advertise through direct mailings to all residents of HRC's seven supportive housing facilities (over 3,000 residents).
- We will give presentations at each Hebrew SeniorLife (HSL) facility.
- We will use the Harvard Catalyst (CTSA) Shared Health Research Information Network (SHRINE) to identify volunteers from Harvard-affiliated hospitals and clinics.
- We will advertise our study within numerous local media outlets, on HRC's Hinda and Arthur Marcus Institute for Aging Research and other websites (*e.g.*, Craig's List), and at www.clinicaltrials.gov.

We will enroll individuals in this study on a rolling basis until 12 participants have enrolled and completed the intervention. Our target population is adults ≥65 years, who have a gait speed <1.0 m/sec and have Mild Cognitive Impairment (Telephone MoCA <19[23]). To maintain adequate participant retention, we will develop personal relationships between participants and study staff, schedule appointments at convenient times, give reminders for each visit, and provide food and beverages during visits. The Marcus Institute has on-site parking for study participants. Based upon our previous experience, we have also budgeted for round-trip transportation by Uber or Lyft for all study visits. We will use precautions to prevent COVID-19 infection, including frequent handwashing, masks, limitation of personal contacts, social distancing when possible, and sanitation of all surfaces and equipment in our facilities. We will compensate our participants for their time.

4.2 Participant Visit Schedule

Once eligibility has been determined at the in-person screening visit, participants will be asked to complete 7 additional in-person visits and 12 brief telephone calls. All study visits will take place at the Clinical Research Laboratory at HRC, Roslindale, MA or at an HRC-affiliated housing site. Free parking or transportation will be provided for all study visits.

Eligible participants who would like participate in our study will be provided with a schedule of all future study visits, including dates and times. A copy of the individualized study visit calendars will be pre-populated within the REDCap Calendar of events. The table below lists the assessments that will be performed at each study visit.

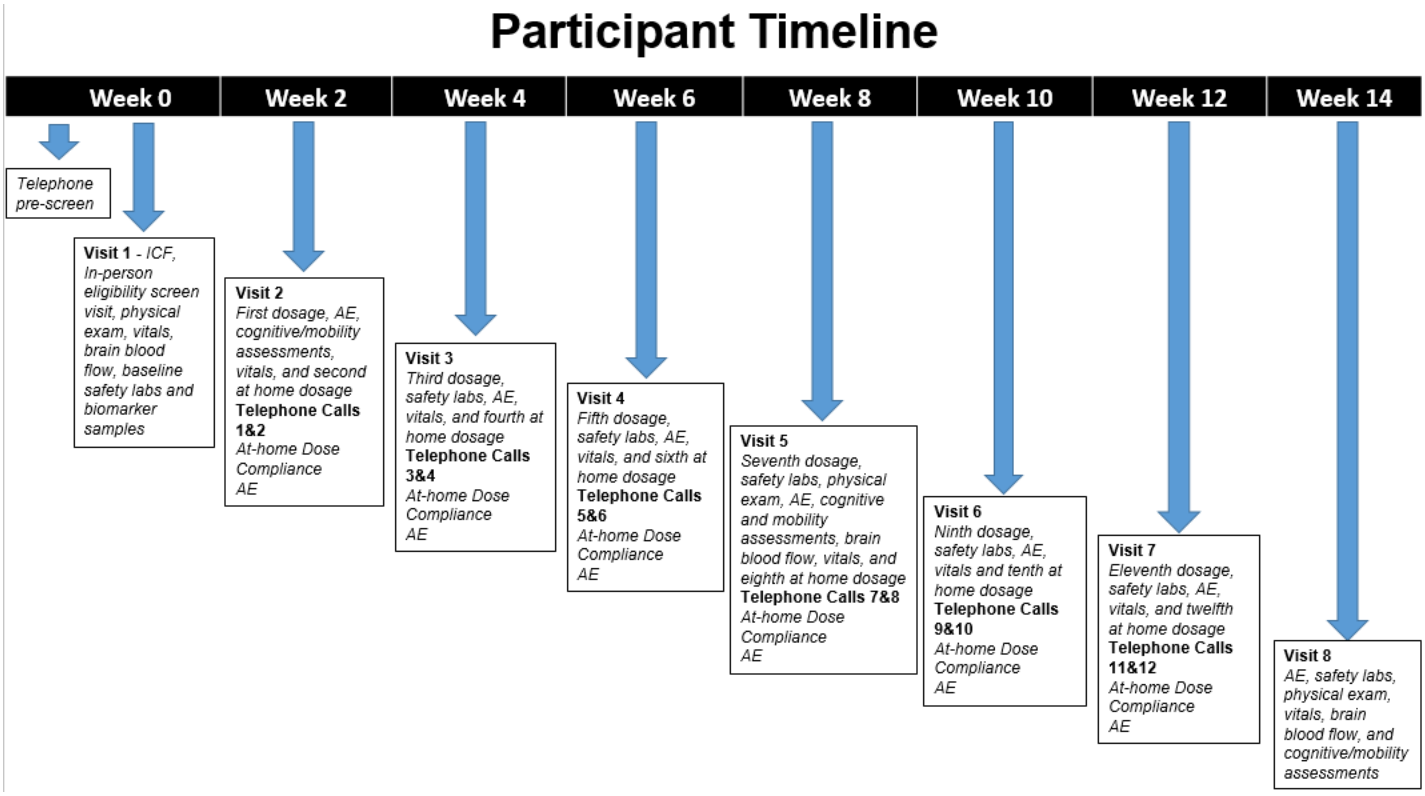
Visits	Assessments and Medication Administration at Each Visit
Telephone screener	We will ask information about: 1. Age 2. Activities of daily living (ADL) 3. Cognitive status (Telephone MoCA) 4. Contraindications or allergies to Quercetin and/or Dasatinib 5. Unstable coronary artery disease (myocardial infarction within 6 months or angina), stroke or transient ischemic attack in the past 6 months, chronic heart failure, current or chronic history of liver disease, neurodegenerative disease including Parkinson's Disease, anemia, or chronic renal disease, or drug or alcohol abuse in the previous 5 years. 6. Hospitalization within 6 months 7. Current medications
Visit 1, Week 0: In-person eligibility, baseline safety labs *[10 +/- 3 days from Telephone screening]*	• Assessments/Activities 1. ICF 2. Physical Exam by study physician, Dr. Lipstiz, or trained medical professional 3. Vital signs and EKG 4. Assessment of gait 5. Health history and current/past medications

	6. Height and weight 7. Blood sample: clinical safety labs and serum senescent biomarkers 8. Urine sample: urinary senescent biomarkers 9. Identify a proxy 10. CBF/NVC protocol
Visit 2, Week 2: Baseline assessment and dosage visit *[14 +/- 3 days from first in-person visit]*	• Assessments/Activities 1. Adverse event baseline assessment (before med administration) 2. Vital signs 3. Gait trials (DT gait protocol– Normal and DT walks), SPPB, TUG, Hand grip strength 4. Full MoCA, TMT, CES-D 5. Suicidal ideation screener 6. Instrumental activities of daily living (IADL) • Medication Administration 1. D+Q administration (first dosage) 2. Provide Home dosage (second day dosage and instructions)
Post –Visit Telephone Calls	1. At-home dosage reminder call and post-visit survey (1 day after visit) 2. Telephone check-in for AE (3-5 days after visit)
Visit 3, Week 4: Dosage visit *[14 +/- 3 days from Baseline Visit]*	• Assessments/Activities 1. Adverse event assessment 2. Vital signs and EKG 3. Blood sample: clinical safety labs 4. Medication Compliance/pill count 5. Suicidal ideation • Medication Administration 1. D+Q administration (third dosage) 2. Provide Home dosage (fourth day dosage and instructions)
Post –Visit Telephone Calls	1. At-home dosage reminder call and post-visit survey (1 day after visit) 2. Telephone check-in for AE (3-5 days after visit)
Visit 4, Week 6: Dosage visit *[14 +/- 3 days from Visit 3]*	• Assessments/Activities 1. Repeat of Visit 3 assessments and activities • Medication Administration 1. D+Q administration (fifth dosage) 2. Provide Home dosage (sixth day dosage and instructions)
Post –Visit Telephone Calls	1. At-home dosage reminder call and post-visit survey (1 day after visit) 2. Telephone check-in for AE (3-5 days after visit)
Visit 5, Week 8: Midpoint assessment and dosage visit *[14 +/- 3 days Visit 4]*	• Assessments/Activities 1. A repeat of Visit 2 assessments and activities 2. Physical Exam by study physician, Dr. Lipstiz, or trained medical professional 3. Blood sample: clinical safety labs 4. EKG 5. CBF/NVC • Medication Administration 1. D+Q administration (seventh dosage) 2. Provide Home dosage (eighth day dosage and instructions)
Post –Visit Telephone Calls	1. At-home dosage reminder call and post-visit survey (1 day after visit) 2. Telephone check-in for AE (3-5 days after visit)
Visit 6, Week 10: Dosage visit *[14 +/- 3 days Visit 5]*	• Assessments/Activities 1. Repeat of Visit 3 assessments and activities • Medication Administration 1. D+Q administration (ninth dosage) 2. Provide Home dosage (tenth day dosage and instructions)
Post –Visit Telephone Calls	1. At-home dosage reminder call and post-visit survey (1 day after visit) 2. Telephone check-in for AE (3-5 days after visit)
Visit 7, Week 12: Final dosage visit *[14 +/- 3 days Visit 6]*	• Assessments/Activities 1. Repeat of Visit 3 assessments and activities • Medication Administration 1. D+Q administration (eleventh dosage) 2. Provide Home dosage (twelfth day dosage and instructions)
Post –Visit Telephone Calls	1. At-home dosage reminder call and post-visit survey (1 day after visit) 2. Telephone check-in for AE (3-5 days after visit)
Visit 8, Week 14: Final follow-up visit	• Assessments/Activities 1. Repeat of Visit 2 assessments and activities

[14 +/- 3 days Visit 7]	2. Physical Exam by study physician, Dr. Lipstiz, or trained medical professional 3. EKG 4. CBF/NVC 5. Blood sample: clinical safety labs and serum senescent biomarkers 6. Urine sample: urinary senescent biomarkers

4.3 Participant Study Timeline

Including the telephone screening, participants will spend a total of 14 weeks in the study. The participant timeline is shown below:



4.4 Compliance and Attrition

At the start of an individual's study participation, he/she will will be given a schedule of their study visits. Visits will be scheduled at a time of day that the participant determines is most convenient for them, and will repeated at the same time for each visit. Transportation will be provided for each visit as needed, snacks will be available, and stipends will be provided for each study milestone. A reminder card will be sent a week before a scheduled visitand/or a reminder call will be made to participants on the day prior to each study visit.

Participants will be tracked throughout their enrollment. Each study visit will be documented. Each study visit will be followed with a brief telephone check-in to ask the participant questions about medication compliance, adverse effects, and their experience during the most recent visit. All calls to the participant and their feedback will be carefully tracked. Notes that may facilitate compliance, such as "call before 10 am", etc, will be kept in participant files.

We will employ specific strategies to maximize participation and compliance:

- ***Positive Framing about Benefits:*** Information will be presented in terms of the possible gains rather than the avoidance of losses as this is a more effective motivational approach.
- ***Feedback and Recognition of Progress:*** Participants will be acknowledged throughout their participation with thank you notes, and will be recognized for their contributions to the study through

regular brief flyers/newsletters such as “Partners in Progress – Mobility and Falls updates”. We will remain in close contact with individuals throughout their participation with follow-up calls each month.

- ***Incentives and Rewards:*** Participants will receive snacks at each visit, cards for achieving milestones, such as birthdays, holidays, etc.; and certificates of completion.

4.5 Study Visits and Assessments

All study visits will take place at the Clinical Research Laboratory at HRC, Roslindale MA or at an HRC-affiliated housing site. Free parking or transportation will be provided for all study visits. A summary of study visits and assessments is provided in the table below. Given that a primary goal of this pilot study is feasibility, we will allow for flexibility for the administration of some assessments at visits, as long as these changes do not impede the scientific interpretation. For example, if the participant is not able to provide a urine sample at the screening visit, they will be allowed to provide a urine sample at visit 2, as long as it is taken before any treatment is administered.

Table. Study Visits and Assessments Timeline

Visits	**0 Telephone Screen**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Weeks		**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**
Procedures:									
Telephone pre-screen script	X								
Telephone MoCA	X								
Katz Activities of Daily Living	X								
Screening/Consent		X							
Medical History		X							
Gait Speed		X				X			X
Comorbidity Score		X							
Height and Weight		X							
Blood Senescent Cells		X							X
Inflammatory Markers		X							X
Urinary SASP Factors		X							X
CBF, NVC		X				X			X
Safety Blood Tests[1,2]		X		X	X	X	X	X	X
Full Physical Exam		X				X			X
Vital Signs[3]		X	X	X	X	X	X	X	X
Electrocardiogram		X		X	X	X	X	X	X
Suicidal Ideation Screener			X	X	X	X	X	X	X
Treatment Administration			X	X	X	X	X	X	
Treatment Compliance			X	X	X	X	X	X	X
Acute Post-Treatment BP[4]			X	X	X	X	X	X	
Symptoms and AEs			X	X	X	X	X	X	X
Cognitive Assessments[5]			X			X			X
Dual Task Gait Speed			X			X			X
SPPB, TUG, Grip			X			X			X
CESD-R			X			X			X
IADL’s[6]			X			X			X

[1]Includes complete blood count with differential, prothrombin time/International Normalized Ratio, a comprehensive metabolic panel (including glucose, calcium, sodium, potassium, bicarbonate, chloride, blood urea nitrogen, creatinine, albumin, total protein, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total and direct bilirubin, glomerular filtration rate, and cystatin C)

[2]As per clinical judgement, additional safety blood tests will be done if warning symptoms are positive on the symptom questionnaire (Appendix J) that are administered during the telephone visits after the treatment administration.
[3]Includes seated blood pressure, postural blood pressure, body temperature, heart rate, respiratory rate, and oxygen saturation
[4]Measure of seated blood pressure 30- and 60-minutes following the treatment administration to detect acute vasodilatory effects of the drugs.
[5]Includes the full 30-point MoCA and the Trail Making Test
AE, adverse events; BP, blood pressure; CBF, cerebral blood flow; CESD-R, Center for Epidemiological Studies Depression Scale- Revised; NVC, neurovascular coupling; SASP, senescence-associated secretory phenotype; SPPB, Short Physical Performance Battery; TCD, Transcranial Doppler ultrasound; TUG, Timed Up-and-Go.
[6]Instrumental activities of daily living (IADL)

Detailed information on study procedures at each visit is outlined below.

Visit 0- Telephone screening (approximately 45 minutes): Volunteers will be asked about cognitive complaints, slowing of gait-speed, impairments in ADL's, current medical conditions, sociodemographics, current medications, and exclusion criteria (see **§3.4**). Participants will also be asked to complete the Telephone MoCA to evaluate cognitive status. A Telephone MoCA score <19, which is indicative of cognitive impairment,[23] is an inclusion criteria of this study.

Telephone Montreal Cognitive Assessment (tMoCA) will be administered by a trained research assistant to determine if the potential participant has Mild Cognitive Impairment (defined as a Telephone MoCA score <19).[23] Individuals with a tMoCA score <10 will be excluded, since it corresponds to a full MoCA score of 14 points,[24] which is indicative of dementia.[25] The assessor will be trained and certified in the conduct of this test.

Visit 1 – In-person screening (approximately 3 hours):
Individuals deemed potentially eligible via the phone screen will complete an in-person screen. All screening assessments, other than the physical exam, will be administered by trained research assistants. Prospective participants will read and sign an informed consent form approved by HRC's IRB, Advarra. A medical history questionnaire will be completed which will ask about current/past conditions, medications, years of education, etc. A 4-meter gait speed will be assessed with a stop-watch over a 4-meter track. Dr. Lipsitz or a trained clinician will conduct a physical exam to determine eligibility. Vital signs and an EKG (See Appendix A for clinical safety exclusion thresholds) will also be assessed. Height and weight will be measured. We will do a bilateral Transcranial Doppler insonation of the MCA to be sure there is a suitable temporal bone window to perform CBF and NVC measurements. If a suitable window is found, the participant will perform the CBF/NVC assessment. Additionally, we will collect up to 60 mL blood sample to check clinical safety measures (~15 mL) and biomarkers of senescence (~45 mL). Urine (~10-15 mL) will also be collected to measure biomarkers of senescence. Eligible participants will identify a proxy for study staff to call if study staff cannot get in contact with the participant. Subjects who meet inclusion criteria will then will be scheduled to return for a baseline assessment, 6 cycles of treatment, and a follow-up assessment.

Medical History: Additional measures to characterize the participants will include age, sex, existing or previous medical conditions, and the Charlson comorbidity score.[30]

Height/Weight will be measured at the screening visit.
1. Height will be measured using a stadiometer.
2. Weight will be measured using a Detecto balance beam scale.

Physical Exam will include a chest, cardiac, and a brief neurological assessment and be performed by the study clinician (or a trained medical professional) at the screening visit to determine eligibility.

Vital Signs (See Appendix A for clinical safety exclusion thresholds) will be performed at each in-person visit.

1. Body temperature, pulse, heart rate, breathing rate, oxygen saturation, seated blood pressure, postural change of blood pressure, and postural change of heart rate) will be assessed by the study doctor or trained personnel.
2. An EKG will be administered by trained personnel and reviewed by the PI and study clinician (Dr. Lipsitz) to evaluate the QTc interval.

CBF and NVC Dual Task: We will assess the CBF response to cognitive activation (N-back) (NVC) while seated and standing from a seated position using protocols previously developed in our laboratory.[31] Subjects will practice the N-Back task prior to initiating recording. Participants will first be instrumented with EKG electrodes, a finometer (to continuously record finger blood pressure), an automatic blood pressure cuff, and the TCD probe affixed on the temporal window to insonate the MCA.
While subjects are sitting comfortably, they will be asked to watch a computer display and complete the following tasks as part of the N-back protocol:

1. Identify X (IDX) task. This is the control condition from which absolute and relative changes in MCA blood flow during the 2-back task are calculated. A series of single letters appears in succession on the projection screen. Subjects are asked to click the right button of a mouse each time they see the letter X. Each letter is displayed for 3 seconds. A 5 second delay between flashing letters, indicated by a blank screen, reduces "tracers."
2. 2-Back: A series of single letters will appear in succession and subjects will be asked to click the right button each time they see a letter that occurred 2 back.

The sequence of testing for each task (IDX and 2-back) is as follows: 55 seconds of blank screen, 95 seconds of IDX followed by 55 seconds of blank screen, followed by 95 seconds of 2-Back, with a 5 second instruction in between each task to indicate which task they should be doing. This sequence will be repeated 2 times for a total of about 6.5 minutes. Each individual's performance during the N-back task is recorded and scored as the percent correct of the total.

Participants will also be asked to complete the following sit-to-stand protocol while instrumented with EKG electrodes etc.:

1. First participants will be asked to sit quietly for 3 minutes while CBF and continuous BP are being recorded.
2. Next participants will be asked to stand for 1 minute while recordings continue.
3. The same procedure will be repeated a second time.

Blood (60 mL) will be collected via serum separator, EDTA, or heparinized tubes by a trained phlebotomist using sterile procedures either at HRC or one of the facilities affiliated with HRC.

1. Approximately 15 mL (~4 mL of blood in EDTA, ~3 mL of blood in a sodium citrate tube, and ~ 8mL of blood in serum separator tubes) portion of the collected blood sample from participants will be used to measure CBC, glucose, liver enzymes, bilirubin, BUN, creatinine, cystatin C, calcium, albumin, prothrombin and international normalized ratio. Samples will be processed, labeled with confidential participant numbers, and measured by HRC clinical laboratory vendor or a reliable clinical laboratory (e.g., Quest Diagnostics) (See Appendix A for clinical safety exclusion thresholds).
2. Approximately ~45 mL (30 mL of blood in EDTA, 5 mL of blood in heparinized tube, and 10 mL of blood in serum separator tube) portion of blood will be collected, processed, aliquoted, and temporarily stored in a -70 degree centigrade freezer. A portion of the 45 mL of blood will be used to isolate cells (e.g., $CD3^+$ T lymphocytes and peripheral blood mononuclear cells) by HRC study staff or a reliable clinical laboratory (e.g., laboratories affiliated with collegiate universities or hospitals). Processed blood samples will be shipped on dry ice to Mayo in batches to measure biomarkers of senescence and aging (e.g., $CD3^+$ T lymphocytes, mitochondrial/nuclear [mt/N] DNA, key microRNA's, cytokines, etc.) in serum and in plasma.

Urine (10-15 mL) will be collected in a sterile container at the screening and final follow-up visits.

1. Urine will be centrifuged and the supernatant will be collected, aliquoted into 0.5 mL tubes, labeled with confidential participant numbers, and temporarily stored at -70 degrees Centigrade; then shipped on

dry ice in bulk to Mayo Clinic for batch analyses of urinary SASP factors (e.g., IL-6, MCP-1, MMPs, etc.)

Visit 2 – Baseline assessments (approximately 2.5 hours):
Approximately 2 weeks later, eligible participants will have a baseline assessment and receive their first dose of D+Q. First, evaluation of symptoms and adverse events (pre-medication administration) will be performed. Vital signs will be measured. A questionnaire on mood (Center of Epidemiology Studies-Depression Scale Revised; CESD-R), instrumental activities on daily living (IADLS), physical function assessments (SBBP, TUG, hand grip strength, and gait speed) and cognitive assessments (the full 30-point MoCA and TMT) will be completed. Participants will under-go a familiarization of the serial subtraction assessment to determine which cognitive task will be implemented in the walking/dual task assessment. Next, the walking/dual task protocols will be completed. Given that newly taking pharmaceuticals has results in increased suicidal ideation, participants will also be screened for suicidal ideation with the P4 suicidality screener.[32] The last activity of the visit will be related to D+Q administration. Participants will be asked to take 100 mg of Dasatinib (1 pill) and 1,250 mg of Quercetin (5 pills) with a glass of water. Research study staff will monitor the participants up to the next hour to evaluate any immediate adverse effects. During this hour, post-treatment seated blood pressure will be measured at 30- and 60- minutes after treatment administration. Finally, participants will be provided the at-home dosage and instructions for consumption of D+Q that will be taken the following day. Breaks and snacks will be provided throughout the visit.

Physical Function will be assessed with three tests: TUG,[152] hand grip strength (via dynamometer) and SPPB.[149]

1. Hand grip strength will be measured with a hand-held dynamometer and we will record the result of each trial to the nearest pound and kilogram. If the difference between any two measures exceeds 6.6 lbs. (3 kg), we will repeat the test once more after a rest period and average the 3 best measurements.
2. The SPPB includes measures of balance (timing of tandem, semi-tandem, and side-by-side stands, test-re-test (T-R-T) correlation=0.97), 4-meter walking speed (T-R-T correlation = 0.89), and ability and time to rise from a chair 5 times (T-R-T correlation = 0.73).[27,33] SPPB validity has been demonstrated by showing a gradient of risk for admission to a nursing home and mortality along the full range of the scale from 0-12.[27] In the EPESE population, summary scores less than 9 independently predicted disabilities in ADL and mobility at 1-6 years of follow-up.[33,34]
3. The TUG[152] requires the participant to stand up from a chair, walk three meters, turn around, walk back and sit down. The average time to complete two separate trials will be recorded. This test has high test-retest reliability and discriminant validity in older adults.[153, 154]

Familiarization will happen just prior to implementation of the walking dual task assessment. Participants will complete a 30-second familiarization of the walking/dual task paradigm. This procedure will 1) determine the cognitive task to be used in the assessment, thereby ensuring that it is not too difficult and/or anxiety provoking to the participant, and 2) minimize the potential for procedural-related learning to influence outcomes. First, we will determine the cognitive task to be used for each participant using a modified procedure[30, 50, 135-137] in which participants are seated in a chair and asked to count backwards from 200 by 3's for 30 seconds. If the participant is successfully able to produce 3-5 correct answers within the 30 seconds they will be instructed to count back by 3's for the walking/dual task assessments for the rest of the study. If the participant is unable to produce 3-5 correct answers within 30 sections, then the participant will be instructed to count back by 1's for the walking/dual task assessment. To maintain consistency at future visits that evaluate the walking/dual task assessment (e.g., Visit 5 and 8), participants will be instructed to count backwards from 200 by 3's or 1's (whichever task was chosen at baseline visit) for 30 seconds in a seated position just prior to the walking tasks.

A Gait Speed and Walking/Dual Task protocol will be completed. Procedures will follow published recommendations [24,139,140] that produce excellent test-retest reliability.[45, 141-145] We have used this paradigm in our laboratory for over ten years. Participants will complete two, 20 meter walks in each of the following conditions:

1. Single task (ST): walking without a cognitive distraction

2. Dual task (DT): walking while counting backwards from a random 3-digit number (either by 3's or 1's; whichever was deemed appropriate during familiarization).

Trial order will be randomized for each assessment and at least 1 min of rest will be provided between trials. The walking trials will be a 20 m distance. Prior to testing, participants will be outfitted with wireless biosensors—each containing a triaxial accelerometer, goniometer and magnetometer—on the sternum, low back, wrists and ankles to record gait kinematics (Mobility Lab™, APDM Inc). Participants will be reminded to walk at their preferred, comfortable pace prior to each walking trial.

The cognitive task will be verbalized serial subtractions from a random three-digit number between 200 and 300, to be provided to the participant prior to each trail. The type of serial subtractions (3's or 1's) will be determined in a familiarization session just prior. Participant responses during each trial will be recorded. We have chosen serial subtractions as the cognitive dual task because: 1) it activates a distributed cortical network including the left dlPFC that is fed by the MCA,[146] 2) it is the most widely used dual task paradigm [24,147] and induces significant and meaningful dual task costs to both postural sway when standing and gait kinematics when walking in older adults with and without a history of recurrent falls, [30,37,38,148] 3) it has been used by our team and will thus enable comparison of current results to those from past studies, and 4) it is reliable and minimally influenced by learning after familiarization.[145] No instructions will be given regarding task prioritization. This approach has been chosen to most closely mimic real-life situations.[24,140,147]

Cognitive assessments will include:

1. Montreal Cognitive Assessment (MoCA, Full 30-point version) will be administered by a trained research assistant. A different, validated version of the MoCA will be used at each assessment to minimize practice effects.[35] Version order will be randomized across participants. The assessor will be trained and certified in the conduct of this test.
2. Executive function using the Trail Making Test (TMT parts A and B, and B minus A to correct for performance speed).[36,37]

Mood and Suicidal Ideation will be assessed. Mood will be measured because it influences performance on clinical tests of physical and cognitive function.[38,39] Suicidal ideation will be assessed throughout the study.

1. We will use the CESD-R,[40] which consists of 20 questions regarding feelings of depression, worthlessness, loneliness, energy level, and fear. The CESD-R has high internal consistency (r=0.90) and a test-retest reliability of 0.51.[41]
2. Suicidal ideation will be assessed using the validated 4-item questionnaire, P4 Suicidality Screener.[32]

Acute Post-Treatment Blood Pressure will be assessed after each administration of study medications. Quercetin is known to have vasodilatory effects. To determine whether Quercetin is acutely acting as a vasodilator, we will measure seated blood pressure before and 30- and 60-minutes after the treatment administration.

Visit 3 – 3rd and 4th Dosages (approximately 2 hours):

Approximately 14 +/- 3 days later, the participant will have their next visit. An evaluation of symptoms and adverse events will be performed using open-ended questions about any events since the last dose, and a questionnaire that asks about previously reported potential side effects. A 15 mL blood sample will be taken to assess clinical safety measures (same as screening). Vital signs and EKG will be measured. We will also assess medication compliance of the previous at-home dose, by asking whether the medications were taken and examining the pill bottles that participants are asked to return. Finally, participants will be asked to take 100 mg of Dasatinib (1 pill) and 1,250 mg of Quercetin (5 pills) with a glass of water. Research study staff will monitor the participants for approximately 1 hour to evaluate any immediate adverse effects. Finally, participants will be provided the at-home dosage and instructions for consumption of D+Q that will be taken the following day.

Visit 4 – 5th and 6th Dosages (approximately 2 hours):

Approximately 14 +/- 3 days later, the participant will have their next visit. An evaluation of symptoms and adverse events will be performed as described above. A 15 mL blood sample will be taken to assess clinical

safety measures (same as screening). Vital signs and EKG will be measured. We will also assess compliance with the previous at-home dose as described above. Finally, participants will be asked to take 100 mg of Dasatinib (1 pill) and 1,250 mg of Quercetin (5 pills) with a glass of water. Research study staff will monitor the participants for the next 1 hour to evaluate any immediate adverse effects. Finally, participants will be provided the at-home dosage and instructions for consumption of D+Q that will be taken the following day.

Visit 5 – 7th and 8th Dosages (approximately 3 hours):
Approximately 14 +/- 3 days later, participants will have a mid-point assessment. An evaluation of symptoms and adverse events will be performed. A 15 mL blood sample will be taken to assess clinical safety measures (same as screening). Dr. Lipsitz or a trained clinician will conduct a physical exam. Vital signs and EKG will be measured. CBF and NVC measurements will be taken. We will also evaluate measures of physical function (SBBP, TUG, hand grip strength, and gait speed), IADLS, and cognitive assessments (MoCA, TMT, and CES-D). Participants will then be asked to take 100 mg of Dasatinib (1 pill) and 1,250 mg of Quercetin (5 pills) with a glass of water. Research study staff will monitor the participants for the next 1 hour to evaluate any immediate adverse effects. Finally, participants will be provided the at-home dosage and instructions for consumption of D+Q that will be taken the following day. Breaks and snacks will be provided throughout the visit.

Visit 6 – 9th and 10th Dosages (approximately 2 hours)
Approximately 14 +/- 3 days later, the participant will have their next visit. An evaluation of symptoms and adverse events will be performed. A 15 mL blood sample will be taken to assess clinical safety measures (same as screening). Vital signs and EKG will be measured. We will also assess medication compliance of the previous at-home dose. Participants will then be asked to take 100 mg of Dasatinib (1 pill) and 1,250 mg of Quercetin (5 pills) with a glass of water. Research study staff will monitor the participants for the next 1 hour to evaluate any immediate adverse effects. Finally, participants will be provided the at-home dosage and instructions for consumption of D+Q that will be taken the following day.

Visit 7 – 11th and 12th Dosages (approximately 2 hours)
Approximately 14 +/- 3 days later, the participant will have their next visit. An evaluation of symptoms and adverse events will be performed. A 15 mL blood sample will be taken to assess clinical safety measures (same as screening). Vital signs and EKG will be measured. We will also assess medication compliance of the previous at-home dose. Participants will then be asked to take 100 mg of Dasatinib (1 pill) and 1,250 mg of Quercetin (5 pills) with a glass of water. Research study staff will monitor the participants for the next 1 hour to evaluate any immediate adverse effects. Finally, participants will be provided the at-home dosage and instructions for consumption of D+Q that will be taken the following day.

Visit 8 – Final Follow-up (approximately 2.5 hours):
Approximately 14 +/- 3 days later, participants will have a final follow-up assessment. An evaluation of symptoms and adverse events will be performed. A urine sample will be collected to measure urinary markers of cellular senescence. A 60 mL blood sample will be taken to assess clinical safety measures (same as screening) and serum biomarkers of cellular senescence. Dr. Lipsitz or a trained clinician will conduct a physical exam. Vital signs and EKG will be performed measured. CBF and NVC measurements will be assessed. We will evaluate IADL's, measures of physical function (SBBP, TUG, hand grip strength, and gait speed) and cognitive assessments (30-point MoCA, TMT, and CESD-R). Breaks and snacks will be provided throughout the visit.

Telephone Reminders and Follow-ups (takes approximately 5-10 minutes each, 1-2 hours total)
Participants will be called prior to each in-person visit to remind the participant of the scheduled visit, provide brief instructions for the visit, and perform a telephone COVID screen if necessary. The participant will also be called the day of each at-home dosage administration (i.e., the day after Visits 2 -7), and approximately 3 +/-2 days after each in-person dosage visit (i.e., Visit 2-7). During these calls participants will be asked about medication compliance with at-home dose, visit satisfaction, side effects, and/or symptoms.

4.6 Drug Intervention

Dasatinib (D) is a chemotherapeutic agent primarily used for the treatment of Chronic Myeloid Leukemia (CML). It is a tyrosine kinase inhibitor that has been shown to reduce the abundance of senescent cells in animals and humans.

Quercetin (Q) is a safe, over-the-counter health promotion product with anti-inflammatory and antioxidant properties that is commonly used in doses similar to ours for the prevention of cancer, cardiovascular disease, diabetes, and infections. It is a flavonoid that has also been shown to reduce the abundance of senescent cells in animals and humans.

Treatment Regimen

Eligible participants will be asked to take D+Q for 2 consecutive days every two weeks. This cycle will be repeated 6 times during the 12 week study duration. As a result, participants will consume a total of 12 doses of D+Q. Each daily dose consists of 100 mg of Dasatinib and 1,250 mg of Quercetin. The Dasatinib comes in a 100 mg tablet, while the Quercetin comes in 250 mg tablets. Thus, there will be 1 pill of Dasatinib and 5 pills of Quercetin for each daily dose.

Preparation and Packaging

The preparation and packaging will be carried out by the research pharmacy Johnson Compounding in Waltham MA (approximately 14 miles from HRC). Johnson Compounding will purchase 100 mg tablets of Dasatinib that is manufactured by Bristol Myers Squibb and 250 mg tablets of Quercetin manufactured by Thorne Research. The investigational products for this study will be delivered to and managed by Johnson Compounding Pharmacy according to FDA-approved procedures. When an eligible participant is enrolled in our study, Dr. Lipsitz and/or study staff will notify Johnson Compounding with the subject name, confidential subject ID number, date of birth, as well as information on allergies and current medications (disclosure of participants' PHI to Johnson Compounding is allowed pursuant to the HIPAA authorization language in the informed consent document) and Dr. Lipsitz will write a prescription for that individual. The subject's name and date of birth will be placed on the bottle to assure that the medication is dispensed to the correct participants' confidentiality. Dr. Lipsitz is certified by the Massachusetts Controlled Substances Registration (MCSR) Board to Use Controlled Substances and Investigational New Drugs in Research. Each cycle, a participant's two-day dose will be bottled by Johnson Compounding (e.g., 1 bottle will contain two, 100 mg tablets of Dasatinib and 1 bottle will contain ten, 250 mg capsules of Quercetin, labeled with the participants' name and date of birth, and instructions). Every label will include a statement that these products are for investigational use only. The filled prescription bottles will be either picked up by study staff or delivered to our laboratory via FedEx or other courier prior to the scheduled in-person visits.

Receiving, Storage, and Dispensing of Study Medications at HSL

Throughout the study, *all study drug disposition and accountability will be tracked using a tracker modeled after the Study Drug/Investigational Product Tracker* (See Appendix C for sample form) provided by the NIA Clinical Research Toolbox which will require date, time, and signature of study staff. All of the study medications will be stored at room temperature 68° to 77°F (20° to 25°C) in a locked laboratory cabinet at HRC.

At the end of each study dosage visit (Visits 2-7) a trained study staff member will dispense 1, 100 mg tablet of Dasatinib from the participant's corresponding pill bottle and 5, 250 mg tablets of Quercetin from the participant's other corresponding bottle. The Study Drug/Investigational Product Tracker will be filled out accordingly by study staff (See Appendix C for sample form provided by the NIA Clinical Research Toolbox) to evaluate study drug disposition and accountability. The participant will be asked to take the study medications (100 mg Dasatinib and 1,250 mg of Quercetin) with a glass of water. Participants will be monitored for an hour by a study staff member, to evaluate any possible acute adverse effects. Any adverse or serious adverse events will be logged on forms that will be modeled after those provided by the NIA Clinical Research Toolbox (See Appendix E&F for sample forms). The monitoring period and any adverse effects will also be recorded in a study monitoring log. Study staff will also fill out a Compliance Log (See Appendix D for sample form),

modeled after the Compliance Log provided by the NIA Clinical Research Toolbox, throughout the study to measure compliance with the study medications.

The remaining pills in the two bottles (one, 100 mg tablet of Dasatinib in one bottle and five, 250 mg tablets of Quercetin in another bottle) are the participant's next day dose. The bottles will be given to participants to take at home with appropriate instructions for storage and administration. All participants will be asked about compliance via telephone calls and study staff will fill out the Compliance Log (See Appendix D) to monitor compliance with study drugs. Participants will be asked to also indicate the time of each dose. Any unexpected mishaps with study medications (e.g., dropped or lost pill) will also be logged.

Return or Destruction of Study Drug

Participants will be asked to bring back the pill bottles (empty or with any remaining study medications tablets if they did not take them). The amount of drug returned and drug remaining will be logged and stored in a locked cabinet in the laboratory at HSL until disposal.

At the completion of the study, there will be a final reconciliation of drugs shipped, drugs dispensed, drug returns, drugs lost, and drugs remaining. This reconciliation will be logged in the Study Drug/Investigational Product Tracker (modeled after Appendix C) and will be signed and dated. Any discrepancies noted will be documented and investigated, prior to return or destruction of unused study drug. Any returned or unused drugs will be destroyed on-site by research staff by placing pills in commercially available drug deactivation and disposal pouches or returned to Johnson Compounding for proper disposal. Drugs destroyed will be documented in the study log files accordingly.

Participant Compliance Monitoring

Participant compliance with the study medications will be monitored in three ways:

1. During the in-person study visit and follow-up telephone calls, study staff will monitor and log compliance of study medications on a Compliance Log (See Appendix D for sample form).
2. Participants will be asked to return their pill bottles with any remaining tablets they did not take on their next visit.
3. The Advarra CRO will monitor this process and its documentation to help assure compliance with good clinical practice and FDA regulations.

4.7 Informed Consent

All interested individuals will be asked to provide verbal consent to complete an initial eligibility screen during a phone conversation with study personnel. Potentially eligible participants will then schedule an in-person screening visit. Potential participants may be sent by email or conventional post (per request, and according to their preference) a copy of the informed consent form for them to review at their own pace prior to the in-person screening. Written informed consent will be obtained by study personnel at the beginning of the in-person screening visit.

4.8 Participant Withdrawal

Any participant who expresses a desire to discontinue participation in the study will be withdrawn at their request immediately. If during the course of their study enrollment, a participant develops a new medical condition that would contraindicate further participation in the study, as determined by a study physician (Dr. Lipsitz), the participant will be informed of this and withdrawn from the study. All data collected prior to withdrawal will be maintained in the study data set.

A subject may be withdrawn from the study prior to completing all of the study related procedures due to the following conditions:

- Subject safety issues

- Failure of subject to adhere to protocol requirements
- Disease progression
- Subject decision to withdraw from the study (withdrawal of consent)

Withdrawn subjects may not reenter the study unless there are extenuating circumstances (e.g. family emergency or required travel out of town) that interfere with the start of the study before any medications are administered. In this case, they may be scheduled to start over again.

Throughout the study, participants will undergo routine physical exams that includes an evaluation of the participant's vital signs and the electrical conductivity of the heart (i.e., EKG). Participants will also have their blood evaluated for relevant safety markers. Thresholds for the safety measures (vital signs, EKG, and blood values) are outlined in Appendix A. If participants meet any of the safety thresholds outlined in Appendix A, the study doctor will determine if the participant will be allowed to continue with the study based on their clinical judgment, as well as input from the Data Safety Monitoring Board.

4.9 Methods to Protect Participant Privacy

The following are the planned procedures for effectively protecting against and minimizing loss of participant privacy:

1. Phone screening will be conducted in a private office space.
2. Study visits will be conducted in private rooms located within the laboratory.
3. Each participant will be given a unique study identification number and data will not include any of the participant's PHI.
4. All participant-identifying information will be stored and managed on a secured database server. The information will be password protected.
5. Participant confidentiality will be maintained in accordance with Health Insurance Portability and Accountability Act (HIPAA) regulations.
6. Only the PI, study personnel, and laboratory personnel approved by the IRB and authorized to view PHI will have access to the information.
7. PHI will not be used during discussion, presentation or publication of any research data.
8. Files containing PHI data collected for recruitment and screening purposes will be kept in locked, secured filing cabinets accessible only to designated study personnel (research assistants and investigators)

4.10 Minimization of Bias

Since participants will serve as their own controls, there is no inter-subject bias. Moreover, some of the data will be gathered using instruments (e.g., Transcranial Doppler) that cannot be influenced by preconceived assumptions. Additionally, to minimize analyst bias, biomarkers will be de-identified and analyzed by technicians unfamiliar with the participants or study phase. Finally, data will be analyzed by investigators who are blinded to participant identity.

CHAPTER 5: TRAINING

Procedures to ensure scientific rigor: A manual of operations will be created with standard participant instructions for each question and assessment. All research staff will review and sign the Site Signature Log – Delegation of Authority Log (See Appendix G) provided by the NIA Clinical Research Toolbox to confirm their responsibilities related to the study. During startup, staff will undergo intensive training, and all training sessions will be logged and signed accordingly. They will conduct all study procedures on 4-5 older adult volunteers (more if necessary) with oversight from the PI to ensure consistency of raters and equipment setup. Quality checks will be done every six months throughout the data collection period.

Training will be based on standardized materials developed for the study, and coordinated by the Project Director. Well-established tests of cognitive function will be administered to characterize critical functions

relevant to several hypotheses being tested in this project. Every six months, the staff will undergo training review and quality checks on all assessments and drug distribution protocols. Additionally, any time there is an amendment to the study protocol, the change will be logged on the Protocol Log (See Appendix H). All study staff will be provided a summary of the protocol modifications (See example in Appendix I) and under-go re-training for the new protocol. The date, duration, and certification of all training will be documented and signed by the Principal Investigator on the appropriate training logs.

CHAPTER 6: DATA MANAGEMENT AND QUALITY

6.1 Data Management

All data collected for analysis will be de-identified and assigned a unique study number. Data collection forms will also be kept in a locked file cabinet in the office of the Dr. Lipsitz (PI) at Hebrew SeniorLife. Data will be entered and stored on a password-protected secure server at HRC.

The Institute for Aging Research primarily employs the REDCap system to facilitate data management operations. REDCap is a full-featured clinical trials data management system (DMS) accessible to data entry and data analysis workstations using secure Web technologies. The REDCap product is developed and maintained by Vanderbilt University in cooperation with REDCap Consortium members, including HRC. HSL hosts and maintains a dedicated instance of REDCap for use across our research enterprise. Each research study is provided separate project workspace in which all of the study data are stored in a MySQL relational database on the private corporate network behind several firewalls and located physically within the HSL data center.

6.2 Participant Tracking

Each recruited participant will be tracked closely throughout study enrollment. A study events calendar will be created within the REDCap database and interfaced with a “Study Hub” developed by the Marcus Institute data management team. Any outstanding or incomplete visits will be accessible in real time to the project director and study team. The study team will maintain regular communications with each study participant throughout enrollment, through regularly scheduled follow up calls, and established retention strategies will be used as discussed in section 4.4.

6.3 Outcome measures

Name	Type	Timeframe	Brief description
Feasibility and Safety	Primary	Throughout the entire study	a) the number of volunteers needed to be screened to identify eligible participants, b) the number and type of protocol deviations necessary to assure participant comfort and safety (reported to the IRB), c) the frequency of possible adverse drug effects, and d) compliance with medication administration.
Cerebral blood flow and Neurovascular coupling	Primary	Screening, 8, and 14 weeks	This metric assesses the ability of the brain to increase blood flow in response to posture change and a cognitive task.
Executive Function (Trails B minus A)	Primary	Baseline, 8, and 14 weeks	This metric assesses executive cognitive function and is corrected for response time.
Gait speed	Primary	Screening, 8, and 14 weeks	This metric assesses the ability to control gait. It is performed without a distracting cognitive task.

SPPB: Short Portable Performance Battery	Secondary	Baseline, 8, and 14 weeks	This test assesses physical performance, including gait, balance, and strength to perform a chair stand.
TUG: Timed Up and Go	Secondary	Baseline, 8, and 14 weeks	This is a timed test of mobility, including standing from a chair, walking 20 feet, and turning.
Grip strength	Secondary	Baseline, 8, and 14 weeks	This test measures grip strength using a hand dynamometer.
Gait speed during cognitive task	Secondary	Baseline, 8, and 14 weeks	This test measures gait speed in response to a cognitive task.
Senescent CD3 cells expressing $p16^{INK4A}$	Secondary	Screening and 14 weeks	This measures the number of senescent CD3 lymphocytes in blood.
SASP factors in blood and urine	Secondary	Screening and 14 weeks	These assays measure senescence associated biomarkers in blood and urine, including IL-1α, IL-6, and MMP-9 and MMP-12.

6.4 Statistical Design and Power

Sample Size Considerations

This project will enroll 12 individuals who will be assessed before, during, and following the 12-week D+Q intervention. The proposed sample size is motivated by the need to make resource assessments in the design of a subsequent RCT of D+Q. We anticipate screening at least two and possibly many more individuals for every potential participant who is eligible and advances to enrollment. Under conservative assumptions we will be able to estimate the proportion of participants screened who are eligible and advance to enrollment to within 0.20 using an 80% exact binomial confidence interval, the upper bound of which will be used in planning the subsequent trial. We will additionally utilize data obtained in this pilot to similarly estimate the variability of outcomes measures and differences attributable to administration of D+Q; again using an 80% confidence interval, we will be able to estimate the standard deviation of continuous measures including CBF and gait speed to within 0.3 standardized units. The design is not intended to provide sufficient data to test the efficacy or effectiveness of D+Q on endpoints relevant for Aims 2 and 3. However, prior small human studies have demonstrated surprisingly robust relationships. For instance, a recent human study of only 9 subjects by the Kirkland group[42] successfully demonstrated that D+Q reduced adipose tissue senescent cell burden within 11 days after a single 3 day course of treatment. Furthermore, circulating SASP factors were reduced in these 9 subjects. We therefore anticipate that we will see suggestive evidence of an association with SASP factors and inflammatory biomarkers in serum and urine, and senescent cells in blood, sufficient to motivate moving forward to a larger clinical trial.

Analytic plan

We will assess distributional characteristics of the primary and secondary outcomes. In addition to analyzing the data from all participants enrolled, we will also explore subgroup analysis based on visit attendance and medication compliance. Feasibility endpoints for Aim 1 will be summarized using sample statistics and confidence intervals. For Aim 2, comparison of functional variables from before to during or after D+Q treatment will be performed using plots and summary tables. Paired differences will be obtained for each endpoint and summarized using sample means, standard deviations, and confidence intervals. For Aim 3 correlations between changes in biomarkers of senescence and changes in functional outcomes will be assessed using scatterplot smoothing and summarized using linear or nonlinear regression analyses as appropriate. Though we will be unable to adjust for covariates, the influence of age and sex will be explored through the use of stratification and added variable plotting.

CHAPTER 7: DATA SAFETY MONITORING PLAN

7.1 Participant Risks

The potential risks to study participants include:

Risks Associated with Quercetin: The most common side effects are headache and tingling of the arms and legs. Serious interactions may occur with everolimus and topotecan. Volunteers taking these drugs will be excluded. Interactions that may increase or decrease other drug metabolism may also occur with cyclosporin and drugs metabolized by P450 enzymes CYP2C8, CYP2C9, CYP2D6, and CYP3A4. The potential for interactions and their clinical implications will be carefully reviewed by the PI and Pharmacy before anyone taking these drugs is enrolled in the study.

Risks Associated with Dasatinib: There are several potentially serious side effects with prolonged daily use, but these are largely avoided with intermittent administration over only 2 days. Long-term daily treatment for CML may result in myelosuppression, bleeding (usually associated with thrombocytopenia and serious in <1% of patients), fluid retention (5% after 5 years of follow-up), cardiac dysfunction (<8.5% after 5 years), reversible pulmonary arterial hypertension, QTc prolongation, and dermatologic reactions. Commonly reported adverse reactions in older patients treated daily over a long term for CML include fatigue, pleural effusion, diarrhea, dyspnea, cough, lower gastrointestinal hemorrhage, and appetite disturbance. Less frequently reported adverse reactions include abdominal distention, dizziness, pericardial effusion, congestive heart failure, hypertension, pulmonary edema, and weight decrease. Since participants will receive only 2 doses at a time with 2 weeks' washout between cycles, adverse effects are unlikely to occur, but we will monitor them closely for any potential effects.

Potential drug interactions reported to affect Dasatinib concentrations include strong inhibitors and inducers of CYP3A4, St. John's Wort, and gastric acid reducing agents such as H_2 antagonists or proton pump inhibitors. These medications are not likely to interact significantly with only 2 doses of Dasatinib at 2 week intervals, but participants who need to continue taking them will be excluded. Any side-effects will be closely monitored and reviewed by the study P.I. If needed, research staff will coordinate appropriate care for individuals with adverse effects as per clinical judgment.

Furthermore, Dasatinib has been associated with fetal toxicity. Thus, all participants will be advised of the fetal risks associated with use of Dasatinib. Females of child-bearing potential or males having sex with women of child-bearing potential are required to use an effective method of contraception (e.g., condoms) throughout the duration of the study and for 90 days after the last study dose. Participants who become pregnant, or impregnate someone else while engaged in the study will be asked to notify study staff and their study doctor immediately.

Risks Associated with Quercetin and Dasatinib: Thus far, 3 clinical interventions administering D+Q have been completed. In 14 adults aged 55-84 years with Idiopathic Pulmonary Fibrosis, 3 weeks of 9 intermittent doses of D+Q (NCT02874989) yielded a retention rate of 100% and there were no serious events. There were no changes in body weight, vital signs, or clinical chemistries.[22] The non-serious events reported during this intervention included respiratory symptoms, skin irritation/bruising, and gastrointestinal discomfort. Of note, the dosing strategy we are employing is less frequent (2 out of every 15 days instead of 3 out of every 7 days), to reduce toxicity[2]. In a second clinical intervention, adults with diabetic kidney disease reported that all participants completed intended doses and no serious adverse events occurred.[42] A third and final completed intervention found no complications after 5 consecutive days of administration of D+Q in 64 health middle-aged adults.[43]

Risks Associated with CBF/NVC measurements: The risks associated with CBF/NVC measurements are minimal. There is no known risk associated with the TCD used to measure CBF. The probes used to measure CBF are held in place by a headband, which may cause minor discomfort from its pressure placed around the head. The electrode patches that will be placed on the participant to measure the EKG could cause stickiness, skin irritability, and slight discomfort. As with the other cognitive assessments, participants may experience mental fatigue and/or anxiety. Participants will be advised that they can refuse to answer any of the questions. It is also possible that some participants may become dizzy or lightheaded when standing from a seated position.

Risks Associated with Assessments of Walking and Physical Function: The proposed walking tests have been adapted from the large-scale, population-based MOBILIZE Boston study (PI: L. Lipsitz) and multiple completed and ongoing clinical studies within the Clinical Research Laboratory at the Hinda and Arthur Marcus Institute for Aging Research. They have been designed to be safe for individuals of varying risk and conditioning levels including older adult fallers. The physical activity associated with these tests is of low to moderate intensity. Potential risks include strains, sprains, muscle soreness, and light-headedness. In rare instances, more serious side effects such as an injurious fall may occur. For all functional tests, a trained "spotter" will stand behind or close to the subject to provide stabilizing assistance if necessary.

Risks Associated with Mood and Cognition: Risks associated with answering these questions are minimal, but participants may experience mental fatigue and/or anxiety. Participants will be advised that they can refuse to answer any of the questions.

Risks Associated with Blood Draw: Risks associated with a blood draw include discomfort, bruising, and/or bleeding where the needle is inserted. It is also possible that some participants may become dizzy or lightheaded. There is a very small risk of infection at the phlebotomy site. Participants will also be advised to refrain from donating blood at least 8 weeks after the last study visit.

Risks Associated with EKG: The risks associated with an EKG are minimal. The patches that will be placed on the participant to measure the EKG could cause stickiness, skin irritability, and slight discomfort.

7.2 Risk Minimization

General Risk Minimization: The proposed protocol requires 8 visits over 14 weeks and therefore imposes a relatively high participant burden with respect to time and effort. Our study team has a strong track record of successful clinical research requiring similar participation, and retention has been high in these projects. The Clinical Research Laboratory at the Marcus Institute is located near a cafeteria and rest room, and is equipped with comfortable seating, a TV, movies, books, and magazines to keep individuals occupied during rest periods. Several additional strategies will be employed to minimize participant burden and maximize adherence to the protocol. We will:

- Develop a personal relationship between participants and members of the staff.
- Schedule appointments at convenient times with familiar staff.
- Explain to participants all aspects of their participation and follow up. We will demonstrate and practice study procedures before beginning data collection.
- Provide reminders of all appointments and follow-up phone calls.
- Include personal notes in the participant's data file to remember events in the life of the participant; these can be commented on at the next visit (e.g., birthday, birth of a grandchild).
- Provide snacks and lunch during all visits.
- Provide transportation for all visits, if required.
- Provide valet or dedicated on-site parking spaces.
- Compensate participants for visits.

Informed Consent Process: All potential participants will be advised that joining the study is completely voluntary and that they may withdraw from the study at any time. The Informed Consent document will be reviewed with the participant at the start of the first Study Visit, either having them read it or asking them to follow along as the staff reads it. When the staff is confident that the participant is completely familiar with the document and understands all the aspects of the informed consent form, it should be signed by the participant in the presence of the staff member, and should then be signed by the staff member. All consent forms will be double checked to make sure they are properly signed and dated. Copies of completed consent forms will be given to the participant and the original signed document will be kept on file at the Hinda and Arthur Marcus Institute for Aging Research.

Risk Minimization for Older Adults with Cognitive Impairment: To ensure all individuals are of cognitive capacity to provide informed consent and participate safely in the study, we will exclude individuals who have scores on the telephone MoCA that indicate they may be beyond Mild Cognitive Impairment and may have dementia. Unfortunately, the telephone MoCA has only been validated to identify Mild Cognitive Impairment, but not dementia. However, the telephone MoCA scoring has been correlated with the full MoCA score. A score of14 points on the full 30 point MoCA is consistent with a diagnosis of dementia[25] and correlates with a telephone MoCA score of 10 points.[24] Therefore, we plan to use a lower limit of 10 points on the telephone MOCA to exclude people with probable dementia

Risk Minimization Related to Dasatinib and Quercetin: Before each drug administration the following will be done: vital signs, review of study drug compliance and other medication use, adverse event screening, and functional assessment (Gait speed, SPPB, TUG, and grip strength). Safety blood tests will be obtained during each visit and sooner if adverse effects occur prior to these times. See Appendix A for clinical safety thresholds. A research assistant will call each participant the day after drug administration and 3 +/-2 days after each drug administration cycle to question them about symptoms and potential adverse effects. If a participant reports they experienced any new or severe symptoms that have been associated with Dasatinib and Quercetin (Appendix J), an additional safety blood test will be obtained as soon as possible, if appropriate and/or as per clinical judgment.

We will minimize the risk to subjects from this study by excluding those with conditions listed in the exclusion criteria. We will also monitor subjects carefully for adverse effects and abnormalities in blood tests or EKGs that may indicate a safety risk. As noted in the research plan and timeline above, participants will be questioned about side effects 1 day and 3+/-2 days after each two-day treatment cycle. Blood studies and an EKG will also be performed after each dosage visit to detect any adverse hematologic, hepatic, renal, or cardiac effects.

The elimination half-life for Quercetin is 11 hours and for Dasatinib it is 4 hours, so after a few days the drugs are gone, but their effects on senescent cells persist. Although continuous daily doses Dasatinib can cause endothelial dysfunction and edema, this is prevented by the antioxidant effects of Quercetin and is not likely to occur with such short-term administration.

CBF/NVC Risk Minimization: Participants will be permitted to rest between studies to prevent fatigue. Only a trained research staff member will administer the TCD, finometer, EKG and automatic blood pressure cuff. The participants will be informed they can refuse the procedure at any time.

Walking and Physical Function Risk Minimization: For all physical tests, a trained “spotter” will stand behind or close to the participant to provide stabilizing assistance if necessary. Participants will be instructed to stop performing or skip any test that makes them feel uncomfortable. Adequate rest will be given in between each test, and any reusable equipment will be cleaned with disinfectant after each use.

Assessments of Mood and Cognition Risk Minimization: Participants will be advised that they can refuse to answer any of the questions. Participants will be permitted to rest between studies to prevent fatigue.

Blood Draw Risk Minimization: Only a trained phlebotomist will be drawing blood using standard, sterile safety procedures.

EKG Risk Minimization: Only a trained research staff member will administer the EKG. The participants will be informed they can refuse the procedure at any time.

Protection of Personal Health Information: All primary study data will be recorded with computer tablets on electronic case report forms (CRF) or as digital files generated from laboratory equipment. All data recording will be in accordance with procedures and guidelines outlined in the study’s Manual of Operations (MOO) authored by the study team. Participant confidentiality will be maintained by recording subject data using a unique subject identifier. Identifiable data, such as contact information and medical record numbers, will be

recorded and stored separately from the clinical study data. Any paper-based study material and any identifiable data will be kept separate in a locked file cabinet accessible by authorized study staff only. Only the study staff directly responsible for the data collection and the safety of the participant will have access to identifiable information. All electronic CRF data will be stored securely in an electronic data capture and management system. Raw electronic instrumentation data will be organized and saved on a private network file dedicated to the research project. Only those listed on the approved IRB protocol will have access to subject data. Subject data will be coded and locked in a file cabinet in a locked office. Identifying information will not be used during discussion, presentation or research publication. All documents and electronic data will be archived for a minimum of three years, or as required by the IRB and federal regulations, after the completion of the clinical trial. The study will be registered at clinicaltrials.gov. The Principal Investigator will obtain a Massachusetts Controlled Substance Registration (MCSR) from the Department of Public Health to be certified to dispense the study medications.

The Hinda and Arthur Marcus Institute for Aging Research employs the Research Electronic Data Capture (REDCap) system for data capture and data management operations. REDCap is a full-featured clinical trials data management system (DMS) accessible to data entry and data analysis workstations using secure Web technologies. While REDCap can be used to collect virtually any type of data (including 21 CFR Part 11, FISMA, and HIPAA-compliant environments), it is specifically geared to support online or offline data capture for research studies and operations. REDCap is developed and maintained by Vanderbilt University in cooperation with REDCap Consortium members, including HRC. HSL hosts and maintains a dedicated instance of REDCap for use across our research enterprise. Each research project is provided separate workspace in which all of the study data are stored in a MySQL relational database on the private corporate network behind several firewalls and located physically within the HSL data center.

7.3 Adverse Events Collection and Reporting

Any adverse or serious adverse events will be logged using forms either provided by or modeled after the form that are provided by the NIA Clinical Research Toolbox (See Appendix E&F).

<u>Definition of an Adverse Event</u>
An adverse event is any untoward medical occurrence in a participant, whether or not it is causally related to the study. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the study. Adverse events will be recorded on the appropriate case report forms and source documents. The investigator and/or trained staff member will evaluate all adverse events as to their severity and relation to the test article. The severity of adverse events will be graded as follows:

Mild: Awareness of a sign or symptom but easily tolerated.
Moderate: Discomfort sufficient to cause interference with usual activity or to affect clinical status.
Severe: Incapacitating with inability to do usual activity or to significantly affect clinical status.
Life Threatening: The participant was at immediate risk of death from the adverse event as it occurred.

The Investigator will also assess the relationship of any adverse event to the study, based upon available information, using the following guidelines:

0 = Unlikely: No temporal association, or the cause of the event has been identified
1 = Possible: Temporal association, but other etiologies are likely to be the cause; however, involvement of the study procedures cannot be excluded.
2 = Probable: Temporal association, other etiologies are possible, but not likely.

To determine the attribution and temporal association of an adverse event we will consider the following:

1) Whether the symptom has been previously associated with the study medications as listed in Appendix J.
2) Whether the participant reports they have experienced the same symptom prior to the study intervention.
3) Whether the symptom occurred and resolved within 24 hours of taking the study medication.

The PI and study doctor, Dr. Lewis Lipsitz, will consider the symptom according to the conditions stated above and determine temporality as per clinical judgment. The PI will consult the DSMB members as needed.

Definition of a Serious Adverse Event

A serious adverse event is any experience that results in any of the following outcomes:

- Death
- Is life-threatening
- Inpatient hospitalization or prolongation of hospitalization

A persistent or significant disability/incapacity. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Adverse and Serious Adverse Event Reporting

There is a potential for adverse events and incidental findings during this study. A structured questionnaire asking about adverse events will be assessed during and within 3 days following all visits. However, when any adverse has been identified, the study team will take appropriate action necessary to protect the study subject and then complete an Adverse Event form that is modeled after the adverse event tracking form from the NIA Clinical Research Toolbox (See Appendix E for sample form). This form requires Principal Investigator review and signature. After review by the Principal Investigator any adverse event will be reported to the IRB, DSMB, and FDA as appropriate.

If a serious event occurs, it will be brought immediately to the attention of the Principal Investigator who will examine the participant, decide if immediate treatment is necessary, initiate such treatment at the Beth Israel Deaconess Medical Center Emergency Room or appropriate hospital or urgent care setting, contact the primary care physician, and notify the IRB, DSMB, and FDA as appropriate. The Serious Adverse Event form (See Appendix F) that is provided by the NIA Clinical Research Toolbox will be completed, which requires Principal Investigator review and signature

Unanticipated problems or adverse events will be reported according to Advarra's IRB written guidelines for interventional studies. Unanticipated problems and serious adverse events that are probably, possibly, or definitely related to the study will be reported as soon as possible from the time of learning of the event, but reported within 10 days to Advarra's IRB per Advarra IRB guidelines. Advarra will be provided a written report submitted and a submission of the incident via the eIRB system. This form will record any adverse symptoms and/or study protocol deviations. Study staff will reference Appendix K (Subject Safety Event Reporting Decision Chart) provided and updated regularly by Advarra to determine whether an event needs to be reported to the Advarra IRB.

All other adverse events/study incidents will be logged on an Adverse Event log and reported to the FDA every quarter.

For less serious or incidental findings the Principal Investigator will speak with the participant about the finding, suggest appropriate follow-up, and if necessary, provide a letter describing the findings and need for follow-up.The Principal Investigator will also speak with the participant's primary care provider if the participant gives permission to do so. If at any time the participant cannot be reached, the PI will contact the proxy the participant identified at Visit 1. Similarly, if the participant has a MoCA score or physical findings that are of concern as per clinical judgment, the PI will review the result, determine if the participant is in need of clinical follow-up, and if so, inform the participants about whom to contact.

Safety and emergency procedures

Situation	Immediate Notification Process	Event Follow up Plan, Documentation of Event, and Event Reporting	Data Management and Storage

Adverse Event occurs at a Study Visit ***Implement Safety/Emergency Procedures as indicated***	Project Director/Study nurse or PI Notified PD -TBD PI– Dr. Lew Lipsitz Medical coverage Office: 617-971-5318, Cell: 617-470-5323; Covering MD within the Marcus Institute (when Dr. Lipsitz is not available)	Project Director/PI will follow-up with Participant *Any adverse event or unanticipated problem that occurs at any time will be reported to the HSL IRB, the DSMB, the FDA, and the NIA in compliance with established guidelines.* *MedDRA coding: System Organ Class (SOC) and Preferred Term (PT) will be used for coding of all reported events*	All Adverse Event Tracking data and Adverse Event data will be entered into the Redcap data base. Adverse event paper forms will be stored in a locked file cabinet
Adverse Event reported at the Visit Follow up Survey			
Adverse Event reported at the telephone follow-up visits			

Any adverse events that take place during testing will be reported by the PI, Dr. Lewis Lipsitz, Director of the Marcus Institute for Aging Research, Professor of Medicine at HMS and Chief of Gerontology at BIDMC and recorded in the database. Dr. Lipsitz will have ultimate responsibility for monitoring participant safety in the trial. The investigators will be responsible for reviewing each adverse event in a timely fashion, and reporting all incidents to the DSMB in accordance with the established DSMB charter, and preparing a summary report. Any adverse events will be reported to the HRC IRB according to written guidelines.

7.4 Participant and Study Stopping Rules

Participant Stopping Rules: As outlined in section 4.8 Participant Withdrawal, participants that meet the identified clinical safety thresholds, will be evaluated by the study doctor to determine continuation of the study. Similarly, if a participant experiences any adverse event that is deemed “severe” as outlined in section 7.3 (Adverse Events Collection and Reporting) their continuation in the study will be determined by the study doctor, with guided input from the DSMB. Additionally, if a serious adverse event (SAE) occurs, it will be carefully reviewed by the study doctor and the DSMB, and appropriately reported to the FDA. Any report of a serious adverse event (SAE) that is thought to be directly related to the study drugs or study procedures, will result in the participant’s discontinuation from the study.

Study Stopping Rules: Similar to the participant stopping rules, all serious adverse events (SAE) will be carefully reviewed by the study doctor and the DSMB, and appropriately reported to the FDA. The DSMB will review each SAE and determine if study termination is warranted.

7.5 Sponsor–Investigator Reporting: Notifying the FDA

The sponsor-investigator (Dr. Lipsitz) will report to the FDA all unexpected, serious suspected adverse reactions according to the required IND Safety Reporting timelines, formats, and requirements.

Unexpected fatal or life threatening suspected adverse reactions where there is evidence to suggest a causal relationship between the study drug/placebo and the adverse event will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A no later than 7 calendar days after the sponsor-investigator’s initial receipt of the information about the event.

Other unexpected serious suspected adverse reactions where there is evidence to suggest a causal relationship between the study drug/placebo and the adverse event, will be reported as a serious suspected

adverse reaction. This will be reported to the FDA on FDA Form 3500A no later than 15 calendar days after the sponsor-investigator's initial receipt of the information about the event.

Any clinically important increase in the rate of serious suspected adverse reactions over those listed in the protocol or product insert will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A no later than 15 calendar days after the sponsor-investigator's initial receipt of the information about the event.

Findings from other studies in human or animals that suggest a significant risk in humans exposed to the drug will be reported. This will be reported to the FDA on FDA Form 3500A, no later than 15 calendar days after the sponsor-investigator's initial receipt of the information about the event.

7.6 Potential Benefits

Participants may not receive any significant health benefit from participation, although some may benefit from knowledge of their health status, as well as potential therapeutic effects of D+Q. We believe that the potential benefits of determining the feasibility of D+Q as a therapeutic intervention to improve mobility and cognitive function as well as mitigate the risk of Alzheimer's disease development in older adults outweigh the above-outlined potential risks to participants, which are expected to be minor, transient, and relatively rare.
The data from this study are expected to provide critical preliminary information regarding the feasibility of using senolytics to improve both physical and cognitive function in older adults at risk of Alzheimer's disease. Results from this study will directly inform the design of future, large-scale efficacy trials.

7.7 Participant Compensation

Participants will be provided a $300 stipend to compensate them for their time spent completing study procedures.

7.8 Data and Safety Monitoring

The Principal Investigator (PI) will be responsible for ensuring each participant's safety on a daily basis. Safety monitoring procedures will be implemented and reviewed by a Data Safety Monitoring Board (DSMB), in accordance with NIA safety policies for human intervention studies. The criteria for discontinuing a participant's participation include the participant's request, as well as any life-threatening or potentially disabling event, including syncope, seizures, an injurious non-accidental fall, hemodynamic collapse, stroke, transient ischemic attack, dysrhythmia, renal insufficiency, angina, myocardial infarction, anaphylaxis, acute hemorrhage, hospitalization for acute illness, or as per clinical judgment. These adverse events will be recorded and included in the database. If a determination about continued participation cannot be made according to these criteria, the adverse event report will be faxed to the chair of the Data Safety Monitoring Board (DSMB) who will make a decision with members of the Board.

A DSMB will be established for this project. The *Data and Safety Monitoring Board (DSMB)* will act in an advisory capacity to the NIA Director to monitor participant safety, evaluate the progress of the study, review procedures for maintaining the confidentiality of data, the quality of data collection, management, and analyses. This will consist of nationally recognized experts in geriatric medicine, biostatistics, clinical research, geroscience, and/or clinical trials. The chairperson will be an individual who is readily accessible for consultation. At the first meeting of the DSMB, members will review the study protocol and safety-monitoring plan.

Prior to the start of the study the DSMB will review the IRB approved protocol, procedure manual, and informed consent documents, with regard to participant safety, recruitment, randomization, intervention, data management, quality control, and confidentiality. The Board will recommend any necessary changes of the protocol to the PI and will review and approve revisions. The Board will identify relevant data parameters and the format of the information to be regularly reported.

The Board will then decide how often they will meet to review standardized reports over the course of the two year project. They will review the progress of recruitment and retention of participants, compliance with the protocol, and operating procedures. If they raise concerns about safety issues, they may request additional data and propose specific analyses. They will make recommendations to the PIs regarding recruitment, retention, compliance, and safety issues, and will send a written report to the Program Administrator following each meeting. The DSMB will be sent reports of research activity and summaries of safety monitoring information before each meeting.

The DSMB Charter will be reviewed and approved by the Board and the NIA and provides a detailed list of the DSMB responsibilities.

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Appendix A.

Clinical Safety Laboratory Test Thresholds, From Merckmanuals.com/professional/resources/normal-laboratory-values/ American Board of Internal Medicine Laboratory Test Reference Ranges – January 2018

Test	**Parameter**	**Threshold* (Or >20% different than baseline, or as per clinical judgement.)**
EKG	QTc Prolongation	>450 ms (Also evidence of right ventricular enlargement, right atrial enlargement, or right heart strain.)
Blood Measures	Glomerular Filtration Rate	GFR <30 mL/min/1.73 m^2
	Complete Blood Count	WBC <4,000 or >11,000 cells/mcL Neutrophils <1,500 cells/mcL Hbg <9 g/dL Hematocrit <34% Platelets <150 x 10^3/mcL
	Alanine Aminotransferase	>70 U/L (2 x normal)
	Aspartate Aminotransferase	>70 U/L (2 x normal)
	Glucose	>200 mg/dl
	Total Bilirubin	>1.5 mg/dL
	Direct Bilirubin	>0.3 mg/dL
	Blood Urea Nitrogen	>25 mg/dL
	Creatinine	>1.3 mg/dL
	Cystatin C	>1.15 mg/dL
	Calcium	>11, corrected for albumin
	Albumin	<3.5 g/dL, also used to correct calcium level: Corrected Ca = measured Ca + 0.8 (4.0 – serum albumin in g/dL).
	Sodium	>147 meq/L
	Potassium	>5.4 meq/L
	Bicarbonate	>32 meq/L
	Chloride	>108 meq/L
	Total Protein	>7.8 g/dL
	Alkaline Phosphatase	>150 U/L
	Prothrombin Time	>13 seconds
	International Normalized Ratio (INR)	>1.1
Vitals	Temperature	>100.3 ºF
	Seated Blood Pressure	>180/100
	Seated Heart Rate	>100
	Postural Change in Blood Pressure	Systolic blood pressure <100 mmHg or a 20 mmHg decline in blood pressure with symptoms of dizziness, lightheadedness, or near syncope at one minute or three minutes of standing
	Postural Change in Heart Rate	Increase of >25 bpm
	Respiration Rate	>20
	Oxygen Saturation	<92%

Protocol
Appendix B.

Dasatinib Contraindications, Interactions, or Cautions

All contraindications, interactions, and/or cautions will be evaluated by the PI, Lewis A. Lipsitz, MD, as per clinical judgment

- anti-arrhythmic medications
- antipsychotic medications
- anxiolytic medications
- anti-platelet medications
- anti-coagulant medications other than aspirin
- quinolone antibiotics
- CYP3A4 inhibitors or CYP3A4 inducers
- other drugs metabolized by the same liver enzymes as Quercetin or Dasatinib
- antacids
- H_2 antagonists
- proton pump inhibitors
- frequent consumption of grapefruit juice
- frequent consumption/use of St. John's wort
- hypersensitivity to drug/class/component
- pregnancy
- breastfeeding during tx and x2wk after D/C
- pulmonary HTN
- electrolyte abnormalities, uncorrected
- caution in female pts of reproductive potential
- caution in elderly pts
- caution if hepatic impairment
- caution if myelosuppression
- caution if thrombocytopenia
- caution if fluid retention
- caution if cardiopulmonary dz
- caution if congenital long QT syndrome
- caution if QT prolongation
- caution if QT prolongation family hx
- caution if torsades de pointes hx
- caution if ventricular arrhythmias
- caution if bradycardia
- caution if recent MI

- caution if CHF
- caution if cumulative high dose anthracycline tx
- caution if thyroid disorder

Quercetin Contraindications, Interactions, or Cautions

All contraindications, interactions, and/or cautions will be evaluated by the PI, Lewis A. Lipsitz, MD, as per clinical judgment

- quinolone antibiotics
- cyclosporine
- medications changed by the liver (e.g., CYP2C8, CYP2C9, CYP2D6, or CYP3A5)
- medications moved by pumps in cells (P-glycoprotein substrates)
- antihypertensive drugs
- warfarin
- caution if pregnant and/or breastfeeding
- caution if kidney problems

Protocol
Appendix C

Study Drug (IP) Tracker						
Use this form as template to track study drug dispense. All items are required to complete each row.						
Date Received/ Dispensed	**Received By**	**Dispensed To**	**Amount Dispensed**	**Dispensed By**	**Amount Remaining**	**Amount Returned**

Protocol
Appendix D

Study Drug Compliance Log

Protocol: [Protocol name]

Principal Investigator: [Principal Investigator's name]

Site ID: [Site ID]

To be updated at every study contact when the participant receives or returns study drug.

Date Dispensed	Amount Dispensed	Units* Dispensed	Date Returned	Actual Amount Returned	Expected Amount Returned
[Date Drug Dispensed] (dd/mmm/yyyy)	[Amount Dispensed]	[Units Dispensed]	[Date Drug Returned] (dd/mmm/yyyy)	[Actual Amount Returned]	[Expected Amount Returned]
[Date Drug Dispensed] (dd/mmm/yyyy)	[Amount Dispensed]	[Units Dispensed]	[Date Drug Returned] (dd/mmm/yyyy)	[Actual Amount Returned]	[Expected Amount Returned]
[Date Drug Dispensed] (dd/mmm/yyyy)	[Amount Dispensed]	[Units Dispensed]	[Date Drug Returned] (dd/mmm/yyyy)	[Actual Amount Returned]	[Expected Amount Returned]
[Date Drug Dispensed] (dd/mmm/yyyy)	[Amount Dispensed]	[Units Dispensed]	[Date Drug Returned] (dd/mmm/yyyy)	[Actual Amount Returned]	[Expected Amount Returned]
[Date Drug Dispensed] (dd/mmm/yyyy)	[Amount Dispensed]	[Units Dispensed]	[Date Drug Returned] (dd/mmm/yyyy)	[Actual Amount Returned]	[Expected Amount Returned]
[Date Drug Dispensed] (dd/mmm/yyyy)	[Amount Dispensed]	[Units Dispensed]	[Date Drug Returned] (dd/mmm/yyyy)	[Actual Amount Returned]	[Expected Amount Returned]
[Date Drug Dispensed] (dd/mmm/yyyy)	[Amount Dispensed]	[Units Dispensed]	[Date Drug Returned] (dd/mmm/yyyy)	[Actual Amount Returned]	[Expected Amount Returned]

** Examples of units dispensed: tablets, pills, bottles, vials, etc.*

Protocol
Appendix E

Adverse Event Form

STUDY NAME	
Site Number: _____	
Pt_ID: _____	

Has the participant had any Adverse Events during this study? ☐ **Yes** ☐ **No** ***(If yes, please list all Adverse Events below)***

Severity	Study Intervention Relationship	Action Taken Regarding Study Intervention	Outcome of AE	Expected	Serious
1 = Mild 2 = Moderate 3 = Severe	1 = Definitely related 2 = Possibly related 3 = Not related	1 = None 2 = Treatment Stopped 3 = Treatment Interrupted 4 = Reduced Dose 5 = Increased Dose 6 = Delayed Dose	1 = Resolved, No Sequel 2 = AE still present- no treatment 3 = AE still present-being treated 4 = Residual effects present-not treated 5 = Residual effects present- treated 6 = Death 7 = Unknown	1 = Yes 2 = No	1 = Yes 2 = No (If yes, complete SAE form)

Adverse Event	Start Date	Stop Date	Severity	Relationship to Study Treatment	Action Taken	Outcome of AE	Expected?	Serious Adverse Event?	PI Initials & Date
1.									
2.									
3.									

Serious Adverse Event (SAE) Report Form

Protocol Title:
Protocol Number: **Site Number:** **Pt_ID:**

1. SAE Onset Date:

2. SAE Stop Date:

3. Location of serious adverse event (e.g. at study site or elsewhere):

4. Was this an unexpected adverse event?
   ☐ Yes ☐ No

5. Brief description of participant with no personal identifiers:
   Sex: ☐ Female ☐ Male Age:

6. Adverse Event Term:

7. Brief description of the nature of the serious adverse event (attach description if more space needed):

8. Category of the serious adverse event:

   ☐ death – date _____
   ☐ life-threatening
   ☐ hospitalization - initial or prolonged
   ☐ congenital anomaly / birth defect
   ☐ required intervention to prevent
   ☐ permanent impairment (Devices Only)

Serious Adverse Event (SAE) Report Form

☐ death – date _____ ☐ congenital anomaly / birth defect

☐ disability / incapacity ☐ important medical event

9. Intervention type:
   - ☐ Medication (Drug, Biological, Vaccine) or Nutritional Supplement: specify _____
   - ☐ Device: Specify: _____
   - ☐ Procedure/Surgery: Specify: _____
   - ☐ Behavioral/Life Style: Specify: _____
   - ☐ Radiation: Specify: _____
   - ☐ Genetic (gene transfer, stem cell, recombinant DNA): Specify: _____

10. Relationship of event to intervention:
   - ☐ Not Related (clearly not related to the intervention)
   - ☐ Possible (may be related to intervention)
   - ☐ Definite (clearly related to intervention)

11. Was study intervention discontinued due to event? ☐ Yes ☐ No

12. What medications or other steps were taken to treat serious adverse event?

13. List any relevant tests, laboratory data, history, including preexisting medical conditions

14. Type of report:
   - ☐ Initial
   - ☐ Follow-up
   - ☐ Final

Signature of Principal Investigator:_____ Date:

Protocol
Appendix G

Site Signature Log/Delegation of Authority Log

Site Number: _____________

STUDY NAME

The purpose of this form is to: a.) serve as the 'Site Signature Log" and b.) assure that the individuals performing study related tasks/procedures are appropriately trained and authorized by the Investigator to perform the task/procedure. This form should be completed prior to the initiation of any study-related tasks/procedures. *The original form should be maintained at your site in the study regulatory/study binder. This form should be updated during the course of the study as needed.*

Please Print	Obtain Informed Consent	Source Document Completion	Case Report Form (CRF) Completion	Assess Inclusion and Exclusion Criteria	Physical Examination	Medical History	Medication History / Concomitant Medication	Collect Vital Signs	Review Vital Signs and Labs for Clinical Significance	Laboratory Specimen Collection/Shipping	AE Inquiry and Reporting	AE/SAE interpretation (severity/relationship to IP)	Administration of Investigational Product (IP)	IP Accountability	Regulatory Document Maintenance	Administrative	
NAME:	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Other: (please specify)
STUDY ROLE:	SIGNATURE:														INITIALS:		DATES OF STUDY INVOLVEMENT:
NAME:	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Other: (please specify) ☐
STUDY ROLE:	SIGNATURE:														INITIALS:		DATES OF STUDY INVOLVEMENT:
NAME:	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Other: (please specify)
STUDY ROLE:	SIGNATURE:														INITIALS:		DATES OF STUDY INVOLVEMENT:
NAME:	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Other: (please specify)
STUDY ROLE:	SIGNATURE:														INITIALS:		DATES OF STUDY INVOLVEMENT:
NAME:	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Other: (please specify)
STUDY ROLE:	SIGNATURE:														INITIALS:		DATES OF STUDY INVOLVEMENT:
NAME:	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Other: (please specify)
STUDY ROLE:	SIGNATURE:														INITIALS:		DATES OF STUDY INVOLVEMENT:

I certify that the above individuals are appropriately trained, have read the Protocol and pertinent sections of 21CFR 50 and 56 and ICH GCPs, and are authorized to perform the above study related tasks/procedures. Although I have delegated significant trial-related duties, as the Principal Investigator, I still maintain full responsibility for this trial.

Investigator ____ **Date:** ________________________________

Protocol
Appendix H

Summary of Changes (Version # to Version #)

Location of Change	Change/Modification in Version #

Protocol Amendment Summary of Changes Template

Purpose: To support the documentation of changes from one institutional review board (IRB)-approved version of a protocol to the next

Audience/User: The protocol amendment author, who will use the tool to create the summary of changes

Best Practice Recommendations:

Administrative details of template

- Review this template and customize to the specific needs and requirements of the study. Sample text may be updated as needed.
- In the template, the instructions and explanatory text are indicated by *{blue italics}*. Instructional text will also be enclosed in braces to signify this text for screen-readers used by the visually impaired.
- Text enclosed with <> is a placeholder for a specific detail (e.g., <protocol title>); replace as appropriate.
- Remove <> and instructional text before finalizing the document.

Pre-amendment

- It is useful to maintain an ongoing list of potential protocol changes—both administrative changes as well as substantive changes—that are being considered for inclusion in a protocol amendment. Some maintain a working version of a protocol amendment in which the POTENTIAL changes have been tracked in a version of the protocol that is maintained separately from the active version.
- To reduce paperwork and confusion, it is helpful to batch protocol changes together into one amendment when possible.
- The list of potential changes should be vetted through the protocol team, prior to inclusion in the draft protocol amendment that is submitted to the IRB.

Preparing and reviewing the protocol amendment summary document

- Consider IRB-specific guidelines/preferences when preparing the protocol amendment summary document.

- The structure of the protocol amendment summary document may depend on the contents of the amendment. In some cases, it may be most appropriate to list the changes one by one as they appear in the protocol. In other cases, an ordering by conceptual change [e.g., DSMB-requested changes or administrative changes] may be best.
- When possible, protocol section numbers should be referenced. It is also helpful to reference page numbers.
- Include a rationale for each set of protocol changes. Document as “administrative change” when appropriate.
- The protocol amendment summary document should be carefully reviewed and confirmed against the actual protocol amendment immediately before submission. Remember that page numbers change as things are updated in the protocol. It is therefore important to do a quality control check of the section and page numbers.

It is best to submit a pdf of the protocol if you are referencing page numbers. This is because page numbers for pdfs are constant across all computer software and systems, whereas the pagination in MS Word documents is system/printer dependent.

The protocol amendment summary document will be submitted to the IRB, stored in the study files, and accessed by the study team.

It is preferable to maintain both a track-changes and a clean version of the protocol version that is submitted to the IRB.

Tool Revision History

Version Number
Version Date
Summary of Revisions Made:

Version Number
Version Date
Summary of Revisions Made:

Version Number
Version Date
Summary of Revisions Made:

Version Number
Version Date
Summary of Revisions Made:

Detailed Summary of Protocol Changes

Protocol Number:

Protocol Title:

	Version Number	Version Date
Current Approved Protocol	<Version # of most recently approved protocol>	<Date of most recently approved protocol>
Amended Protocol	<Version # of amended protocol being submitted to the IRB>	<Date of amended protocol being submitted to the IRB>

Section and page numbers are references to the *{indicate track-changes version, if that is what you are using}* amended protocol.

1. **<Section Number, Section Title, Page Number(s)>**
   Old Text:

   New Text: *{Include new text, preferably with track changes on to reveal the differences from the previous version of the document.}*

   Rationale for Change:

2. **<Section Number, Section Title, Page Number(s)>**
   Old Text:

   New Text: *{Include new text, preferably with track changes on to reveal the differences from the previous version of the document.}*

   Rationale for Change:

{Replicate above structure as needed for additional changes, ensuring that the numbering is continuous.}
{The item below is a suggested final item that covers all remaining administrative updates that have not otherwise been detailed above.}

3. **Administrative changes:** Minor changes involving grammar, wordsmithing, punctuation, and other editorial changes have been made throughout the document. All are clearly identified in the track-changes version of the amendment.

STAMINA SYMPTOMS QUESTIONNAIRE

STUDY ID ☐☐☐☐ **ASSESSOR ID:** ☐	**DATE** ☐☐/☐☐/☐☐☐ ☐	**Cycle and Visit** ☐ 1B– 1st Cycle Baseline 1M- 1st Cycle Meds Call 1C- 1st Cycle Check-in 2B– 2nd Cycle Baseline 2M- 2nd Cycle Meds Call 2C- 2nd Cycle Check-in 3B– 3rd Cycle Baseline 3M- 3rd Cycle Meds Call 3C- 3rd Cycle Check-in 4B– 4th Cycle Baseline 4M- 4th Cycle Meds Call 4C- 4th Cycle Check-in 5B– 5th Cycle Baseline 5M- 5th Cycle Meds Call 5C- 5th Cycle Check-in 6B– 6th Cycle Baseline 6M- 6th Cycle Meds Call 6C- 6th Cycle Check-in

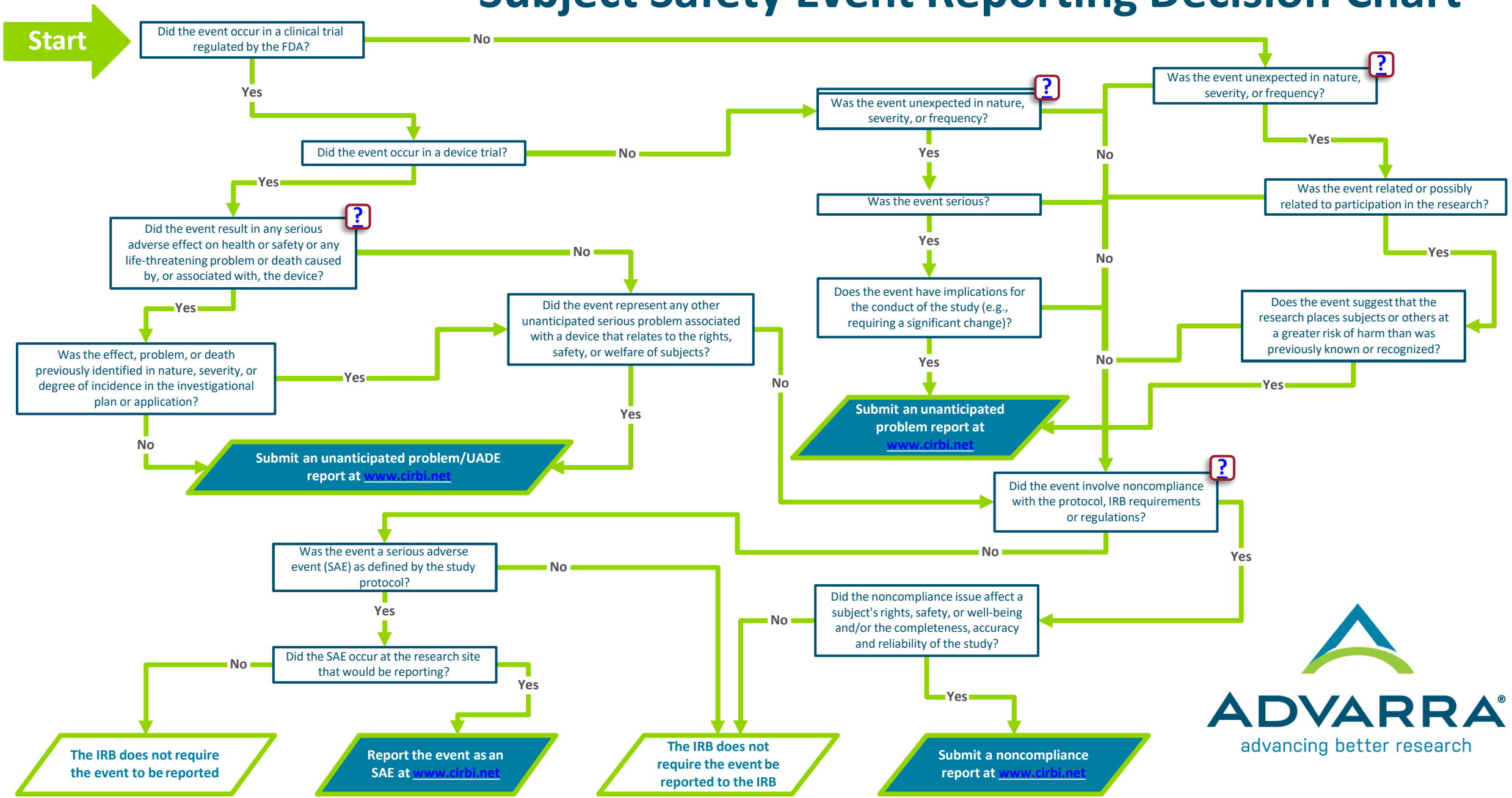
Next is a set of questions about symptoms that you may have experienced. Please answer yes if you have experienced any of the following **NEW** symptoms after taking the study drugs or they are **more severe than usual:**

	0 No	1 Yes	8 Refused	9 DK/ NVR
Fatigue (tiredness)				
Fainting				
Dizziness				
Difficulty Breathing				
Bruising in places other than where blood was drawn				
Coughing				
Skin Rash				
Fluttering Chest Sensation				

Diarrhea				
Blood in Stool				
Loss of Appetite				
Severe Headache				
Tingling/numbness of arms or legs				
Something else I haven't mentioned?				

[IF SOMETHING ELSE IS YES] Please specify	

Subject Safety Event Reporting Decision Chart



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Version 2 2/25/2021

INFORMED CONSENT AND AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION

Sponsor / Study Title:	**National Institute of Aging / "Senolytics to Alleviate Mobility Issues and Neurological Impairment in Aging (STAMINA)"**
Principal Investigator:	**Lewis Lipsitz, MD**
Telephone:	**617-971-5688** **617-470-5323 (24 Hours, emergency only)**
Address:	**Hebrew Senior Life** **1200 Centre St.** **Boston, MA 02131**

Concise Summary of Key Information

The purpose of this research study is to test the use of an FDA approved chemotherapeutic (used to treat cancer) agent (called Dasatinib or Sprycel) and a dietary supplement (called Quercetin) in older adults using low, every-other-week doses for 12 weeks. We want to test if we can re-purpose these drugs to help people with concerns about their memory and mobility. We will include 12 people with mild memory and walking problems who may be at risk of developing Alzheimer's disease in the future.

Other studies have already tested these drugs in people with a severe lung disease, people with chronic kidney disease, and in healthy adults. During this study, the number of times you will be asked to take the drugs is very small compared to the daily doses of Dasatinib used for many months to treat cancer, or the daily doses of Quercetin when used as a dietary supplement for health promotion. These study drugs have been found to be safe in adults with a severe lung disease called pulmonary fibrosis and chronic kidney disease. We now want to test them in older adults with slow walking speed and mild cognitive impairment. Because we will be providing a low dose that you take only 2 days every other week, we do not anticipate major risks.

Participation in this study will take a total of 14 weeks and will require 8 in-person visits. You will be asked to take 100 mg of Dasatinib and 1,250 mg of Quercetin for 2 days every other week for a total of 12 weeks. During the study we will ask you about any symptoms you've had, and to provide blood and urine samples. And finally, we will measure your physical ability (for example your walking) and cognition (for example your memory).

About this Consent Form

Please read this form carefully. This form provides important information about participating in a research study. As a research participant, you have the right to take your time in making decisions about participating in this research and you are encouraged to discuss your decision with your family and your doctor. If you have any questions about the research or any part of this form, please ask us. If you decide to take part in this research, you will be asked to sign and date

this form, and a copy will be provided for you. Please take your time in making your decision as to whether you wish to participate or not. Ask the study staff to explain any words or information contained in this informed consent document that you do not understand or are unsure about. You may also discuss this study with your friends, family, and primary care doctor.

What you should know about a Research Study
Participation in research is voluntary, which means that it is something for which you volunteer. It is your choice to participate in the study, or to decline participation. If you choose to participate now, you may change your mind and stop participating at a later date. Refusal to participate or withdrawal of participation will not result in any penalty or loss of benefits to which you are otherwise entitled such as care by your healthcare provider or negative consequences to your living arrangements.

Purpose of the Research
As people grow older they accumulate old cells in their bodies that stop dividing and produce harmful toxins that can damage organs and cause a variety of diseases. These cells, called senescent cells, cause inflammation, tissue damage, and degenerative processes that can lead to memory loss, mobility problems and even Alzheimer's disease. You are being asked to take part in this study because you are older than 65, you have memory and mobility concerns, and may be at risk of developing Alzheimer's disease. Therefore, you may have these old cells (senescent cells) in your body.

Scientist are developing and testing drugs that can eliminate these senescent cells from the body to prevent diseases like Alzheimer's disease. One of these is a dietary supplement called Quercetin that comes from fruits and vegetables. Another is called Dasatinib (also called Sprycel), which is used to treat certain cancers if taken every day for long periods of time. Dasatinib and Quercetin has been taken by patients with idiopathic pulmonary fibrosis (a severe lung disease) and chronic kidney disease without causing serious adverse events. Dasatinib and Quercetin have improved signs of Alzheimer's disease in animal studies, but these drugs have not been tested in people with memory and mobility problems. Therefore, we want to see if we can re-purpose these drugs in people with memory and mobility problems who may be at risk of Alzheimer's disease so we can test their effects on symptoms, memory, walking speed, mood, and blood flow to the brain. In our study, the use of Dasatinib and Quercetin is investigational. This means that the study drugs have not yet been approved by the FDA for the purpose we are studying, namely, treatment of the pre-stages of Alzheimer's disease. That is why we are conducting this pilot study. A pilot research study is a small study conducted in order to evaluate how practical it is to conduct certain procedures, and to refine the study design for future larger-scale studies. The FDA, which monitors all investigational studies with drugs has given us approval to do this study.

Key Information

1. **How many people will be in the study?**
   A total of 12 people will be in this pilot study. In order to find the 12 people that are able to be in our study, we may need to screen many more because some won't qualify for the study.

2. **How long is the study and how many visits?**
   Each person will be enrolled for 14 weeks, and requires 8 in-person and 12 short telephone calls (10 minutes each) with a study staff member. You can stop participating at any time.
3. **Where are the study visits?**
   Most study visits will take place in our research center located at Hebrew Rehabilitation Center (HRC; 1200 Centre Street, Roslindale, MA 02131). It may be possible to have some of the study visits at one of the HRC-affiliated housing sites.
4. **How often do I take the study drugs?**
   At visit 2, you will be asked to take the first dose of 100 mg of Dasatinib and 1,250 mg of Quercetin (D&Q). You will take another dose of these study drugs the next day at home. The following week you will not have to take any. You will then return to the research center and repeat the two week cycle 5 more times, which will equal a total of 12 weeks. This means you will take 12 doses of D&Q during this study.
5. **How many pills do I take during the study?**
   You will be asked to take 1 pill of Dasatinib and 5 pills of Quercetin 12 times during this study over a total of 12 weeks. You will take the same dose each time you take the study drugs.

Research Procedures
Involvement in this study will require 8 in-person study visits at our research center over 14 weeks. Transportation will be provided if needed. Below outlines each study visit in detail. There are visits that require blood draws. It is okay for you to eat before the blood draw (you don't need to come to the study laboratory fasted). If at any time you feel uncomfortable answering a question or do not want to perform one of the study assessments, you can say so and the assessment will be stopped immediately.

Visit 1 (takes roughly 3 hours): Hebrew Rehabilitation Center, Roslindale
At this first visit, you will learn all the details of the study and you will be given time to ask any questions you might have. If you decide to participate then you will be asked to sign and date the consent form and you will receive a copy to take home with you.

You will be asked some questions about your medical history, your daily activities and medications including dietary supplements you take. You'll have a brief physical exam of your heart and lungs conducted by our study clinician. Vital signs, such as blood pressure, pulse, temperature, respirations, electrocardiogram (EKG), height, and weight will be measured. You will also do a short walking task at your usual walking speed. You'll be asked to have a blood test (about 4 tablespoons will be drawn) to determine if it is safe for you to take the study drugs and determine if you have any old (senescent) cells in your blood. You will also be asked to provide a urine sample to check for old (senescent) cells in your urine. The blood and urine samples will be taken at either HRC or an HRC-affiliated site.

During Visit 1, we will use a Doppler microphone, called a transcranial Doppler, to see if we can measure your brain blood flow. To do this, we will place the microphone at your temple just in front of your ear. In some people, the bone at the temple is so thick that the ultrasound cannot detect the blood flow. This is normal. However, if this happens, we will not be able to enroll you

in the study. If we can detect blood flow, we will measure the blood flow to the brain while you perform a memory task and when you stand up from a seated position.

If you don't qualify for the study, we will send you a letter with the results of your lab work so you can share them with your doctor.

Visit 2: Baseline visit (before any study drugs; takes roughly 3 hours):
Approximately 2 weeks later, you will come back Hebrew Rehabilitation Center for a second study visit. At this visit we will ask you some questions about your health, mood, and if you are currently experiencing any health symptoms. We will measure your vital signs (blood pressure and heart rate) as we did at Visit 1. You'll complete some tests of memory and thinking such as connecting numbers and letters, drawing things, remembering specific words and answering various questions. You will be asked to do some physical assessments, such as walking and balance measures. Your handgrip strength will be measured by asking you to squeeze a handgrip several times. At the end of the visit, we will give you your 1st dose of Dasatinib and Quercetin with a glass of water**.** We will also give you your 2nd dose to take home and instructions on how to take the study drugs the next day.

Visits 3 and 4 (takes roughly 2 hours each):
Approximately 2 weeks later, you will have a third visit. Approximately 2 weeks after the third visit you have a fourth visit. At both visits we will evaluate any **symptoms** (same as Visit 2)**,** perform an assessment of **vital signs and EKG** (same as Visit 1)**,** and provide **study drugs** (same as Visit 2). We will also draw approximately 1 tablespoon of **blood** to see if it is safe for you to continue to take the study drugs.

Visit 5 (takes roughly 3 hours):
Approximately 2 weeks later, you will have a fifth visit where we will evaluate any **symptoms** (same as Visit 2), perform a brief physical exam by our study clinician (same as Visit 1), perform an assessment of your **vital signs and EKG** (same as Visit 1)**,** provide **study drugs** (same as Visit 2), and draw approximately 1 tablespoon of **blood** (same as Visit 3). Additionally we will perform **memory/thinking assessments** (same as Visit 2), **physical assessments** (same as Visit 2)**,** and we will measure your **blood-flow to the brain** (same as Visit 1)**.**

Visits 6 and 7 (takes roughly 2 hours each):
Approximately 2 weeks later, you will have a sixth visit. Approximately 2 weeks after the sixth visit you will have a seventh visit. At both visits we will evaluate any **symptoms** (same as Visit 2)**,** perform an assessment of **vital signs and EKG** (same as Visit 1)**,** provide **study drugs** (same as Visit 2) and draw approximately 1 tablespoon of **blood** (same as Visit 3).

Visit 8 (takes roughly 2.5 hours):
Approximately 2 weeks later, you will have a final visit where we will evaluate any **symptoms** (same as Visit 2), perform a brief physical exam by our study clinician (same as Visit 1), perform an assessment of **vital signs and EKG** (same as Visit 1)**,** and draw approximately 4 tablespoons of **blood** (same as Visit 1). Additionally we will perform **memory/thinking assessments** (same as Visit 2), **physical assessments** (same as Visit 2)**,** and we will measure your **blood-flow to the brain** (same as Visit 1)**.**

Telephone Reminders and Check-ins (takes 5-10 minutes each, approximately 60 minutes total):
Prior to each in-person visit, study staff will call you to remind you of your scheduled visit and we may ask you about recent symptoms. Approximately 1 and 3-5 days after each in-person visit, a study staff member will call you to ask you if you took the most-recent at-home dose of Dasatinib and Quercetin and if you have had any symptoms or side effects that might be related to the drugs.

Visit	Purpose	Procedures	Time	Place*
Visit 1	Screening visit	Blood test, urine sample, brain blood flow with memory test, physical assessments, physical exam, medical history, height and weight, vitals/EKG	~3 hours	HRC
Visit 2, Baseline	Start study drug: 1st & 2nd dosage	Memory/thinking and physical assessments, symptoms questionnaire, vitals and receive study drugs	~2 ½ hours	HRC
Visit 3, Week 2	3rd & 4th Dosage	Blood test, symptoms questionnaire, vitals/EKG, and receive study drugs	~2 hours	HRC
Visit 4, Week 4	5th & 6th Dosage	Blood test, symptoms questionnaire, vitals/EKG, and receive study drugs	~2 hours	HRC
Visit 5, Week 6	Mid-point visit, 7th &8th Dosage	Blood test, memory/thinking assessments, physical exam, physical assessments, symptoms questionnaire, brain blood flow, vitals/EKG, and receive study drugs	~3 hours	HRC
Visit 6, Week 8	9th & 10th Dosage	Blood test, symptoms questionnaire, vitals/EKG, and receive study drugs	~2 hours	HRC
Visit 7, Week 10	Final 11th & 12th Dosage	Blood test, symptoms questionnaire, vitals/EKG, and receive study drugs	~2 hours	HRC
Visit 8, Week 12	Follow-up Visit	Blood test, urine sample, memory/thinking assessments, physical exam, physical assessments, brain blood flow, vitals/EKG, and symptoms questionnaire	~2 ½ hours	HRC

*It is possible some study visits could occur at HRC or an HRC-affiliated facility

Possible Future Use of Biological Specimens or Data
In order to further increase scientific knowledge and enable future research of other age-related conditions, the identifiable samples and/or identifiable private information collected from you during this study may be used for future studies or shared with other researchers. If the study doctor distributes your samples and/or information to other researchers or institutions, your samples and/or information will be labeled with a research code and any personal identifiers will be removed so that no-one will know that they came from you. No additional consent will be requested for the future use of your samples or information.

If you have questions about storing samples or would like to request that samples be removed from storage, please let us know. It is not always possible to remove samples from storage or to retrieve samples from which identifiers have been removed and/or that have already been sent to other investigators. Data and specimens collected before you decide to withdraw your permission for their use, will not be able to be withdrawn because they have not been saved with your name or identifying information attached to them.

If you agree to participate in this study, we will draw at most 4 tablespoons of blood at each visit. Some of your blood will be sent to Mayo Clinic in Rochester, Minnesota to measure the old cells and products of the old cells in your blood. The left over blood (approximately 1 tablespoon) and urine (approximately 1 tablespoon) will continue to be stored in a freezer at Mayo Clinic. The left over blood/urine will not be labeled with your name. It is possible that we will measure other things in the blood/urine in the future. An Institutional Review Board (IRB) must also approve any future research using your blood/urine.

The research that is performed with your blood/urine is not designed to help you specifically. There is no personal benefit to you for agreeing to this part of the research, but it might help people who have diseases at some point in the future. The results of the research performed with your blood/urine will not be given to your study doctor or put in your medical record. The research using your blood/urine will not affect your care. Your blood/urine will only be used for research and will not be sold.

Return of Research Results

During this research we may learn information from the study results that could be important for your health or your treatment; however, we will not share this information with you. We will tell you about anything we discover that could impact your immediate health or decision to stay in the study.

Risks and Discomforts of Participating in the Research

Being a part of any research study comes with some risk. You should discuss the risks below with the study staff. Risks and side effects related to the study visits, study drugs, and study involvement include:

1. Study Drugs
    - All drugs can have side effects. You will be asked to take Dasatinib only two days every two weeks. Each week your body will have a chance to clear Dasatinib before you take the next dose. Long-term daily intake of Dasatinib has been shown to cause adverse effects that include:
        - Low blood cell counts
        - Bleeding problems
        - Fluid retention
        - Heart problems
        - Pulmonary arterial hypertension (high blood pressure in the vessels of your lungs)
        - Skin reactions
        - Fatigue (tiredness)
        - Diarrhea
        - Cough

- Bleeding in the digestive tract
- Appetite disturbance
- Bloating
- Dizziness
- Weight loss
- Tumor Lysis Syndrome, which is caused by the fast breakdown of cancer cells. Tumor Lysis Syndrome can further cause kidney failure and an abnormal heart beat.

Dasatinib can cause other side effects if taken while you are taking certain other medications. If you need to take any of the following medications, and cannot stop them temporarily, you will not be able to be in the study: anti-arrhythmic medications, antipsychotics and anxiolytics, anti-platelet or anti-coagulant medications other than aspirin, quinolone antibiotics, or drugs metabolized by the same liver enzymes as Dasatinib. The study staff will carefully review your medications to check if you are taking any of these. You will not be taking the Dasatinib daily. You will only receive 2 doses every 14 days. Thus, adverse effects are not likely to occur. A study doctor will review all safety measures (symptoms, blood tests and EKG).

- **Quercetin** may cause headaches and tingling of the arms and legs. There are serious interactions that occur with some other medications. To avoid this risk, you will not be eligible if you are taking medications that interact with Quercetin.

2. Blood Sampling
   - You may experience discomfort, bruising and/or bleeding where the needle is inserted to get a blood sample. Occasionally some people become dizzy, lightheaded or feel faint. Infection could occur, but it is rare and therefore unlikely. Frequent donation of blood can result in low iron in your blood (iron deficient anemia). You should not donate blood for at least 8 weeks after completing this study.
3. EKG (electrical activity of the heart)
   - When we measure the electrical activity of the heart, we will place patches (similar to stickers) on your arms and legs that are connected to the heart monitoring machine. When we remove the patches you may experience stickiness, skin irritability, and slight discomfort.
4. Physical Tests
   - Your ability to perform certain physical activities will be measured before and after you take the study drugs.
   - There is a small risk of a fall during the walking and balance tests. A trained “spotter” will be at your side at all times.
5. Brain Blood Flow
   - There is no known risk associated with the machine used to measure blood flow to the brain (Transcranial Doppler ultrasound). This device is similar to a Doppler a doctor would use to listen to a baby’s heartbeats in the womb. The probes used to measure blood flow in the brain are held in place by a headband, which may cause minor discomfort from its pressure placed around the head.
6. Questionnaires and Memory/Thinking Tests
   - During the clinic visits we will ask you a variety of questions that you may feel are boring or wonder why we need this information. Please know that we only collect

information that we feel may be useful to know when studying the effects of Dasatinib and Quercetin. You may become tired during the questionnaires and if this occurs we can take a break until you are ready to continue.

There may also be other side effects that we cannot predict. The study doctor does not know all the side effects that you may experience. Like all investigational drugs, all side effects may not have been identified at this time; some may be mild or others very serious. Everyone taking part in the study will be watched closely for any side effects. It is important that you tell your study doctor when you feel or seem different compared to your usual self while taking part in the study. You should tell the research staff about all the medication, vitamins and supplements you take and any medical conditions you have. This may help avoid side effects and/or other risks.

Reproductive and Other Risks
Females: Taking the study drug may involve risks to a pregnant woman, an embryo, fetus (unborn baby) or nursing infant. If you are of child-bearing potential, you are required to use an effective method of birth control while you are participating in this study and for 90 days after your last dose of the study drug.

Males: If you have sex with a woman of child-bearing potential, you are required to use an effective method of birth control while you are participating in this study and for 90 days after your last dose of the study drug. Acceptable methods of birth control for use in this study are a condom. A condom is required to be used also by vasectomized men with a partner of child-bearing potential to prevent delivery of the study drug through seminal fluid. The study doctor or study staff will discuss this with you. If your female partner becomes pregnant while you are participating in this study or within 90 days after you have stopped taking the study drug, tell your study doctor or study staff immediately.

All records associated with your participation in this study will be confidential. However, because the use of this drug is regulated by the Food and Drug Administration (FDA) and the National Institute of Aging (NIA), agents of the FDA and the National Institute of Aging may have access to these records during the course of their duties. Representatives of Hebrew Rehabilitation Center and the institutional review board, Advarra, reviewing this study will also have access to your file to monitor that the study is conducted properly.

In Case of Injury while Participating in the Research
We will offer you the care needed to treat any injury that directly results from taking part in this research study. If we cannot provide the care directly, we will arrange for the care to be provided to you at a nearby institution. We (and/or the treating provider, as appropriate) reserve the right to bill your insurance company or other third parties, if appropriate, for the care you get for the injury. We will try to have these costs paid for, but you may be responsible for some of them. For example, if the care is billed to your insurer, you will be responsible for payment of any deductibles and co-payments required by your insurer.

Injuries sometimes happen in research even when no one is at fault. There are no plans to pay you or give you other compensation for an injury beyond what is described above, should one occur. However, you are not giving up any of your legal rights by signing and dating this form.

If you think you have been injured or have experienced a medical problem as a result of taking part in this research study, tell the person in charge of the study as soon as possible. The researcher's name and phone number are listed on the first page of this consent form.

Benefits to Participating in the Research
You may not directly benefit from this study, but others may benefit from the knowledge gained in connection with your participation.

Alternative Treatments or Procedures to those Conducted in the Research
This research study is for research purposes only. The only alternative is to not participate in this study.

Confidentiality of Information Collected as Part of the Research
With any research study, there is a risk of a breach in confidentially. This would mean that someone who should not have access to your information may try to find a way to get it. We will do our best to protect your confidential information by giving you a special study identification number that we will include instead of your name, on the research records. Taking part in this research study may involve providing information that you consider confidential or private. Efforts, such as coding research records, keeping the records secure, and allowing only authorized people to have access to research records will be made to keep your information safe.

A Data Safety Monitoring Board, which is an independent group of experts overseeing the study's safety, will be reviewing the data from this study while it is being conducted. This group of experts will not see your name or be able to determine your identity when reviewing your records. All personal information obtained in the study will be kept confidential, and this information will only be available to the research staff and the Advarra Institutional Review Board (IRB). The records identifying your name will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. The results of the study will only be published or presented as group data. No individual participants will be identified. Forms to collect data will be labeled with a unique study number and kept locked in the study office.

Your records may be reviewed in order to meet federal or state regulations. Reviewers may include representatives from the Food and Drug Administration, the National Institutes of Health and its agencies, Hebrew Senior Life representatives and Advarra Institutional Review Board members with oversight responsibility for this study, or others in order to meet regulatory requirements.

Certificate of Confidentiality
The National Institutes of Health (NIH) has issued a Certificate of Confidentiality to further protect your privacy. With this Certificate, the study doctors may not disclose research information that may identify you in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings, unless you have consented for this use. Research information protected by this Certificate cannot be disclosed to anyone else who is not connected with the research unless: there is a law that requires disclosure (such as to report child abuse or

communicable diseases, but not for legal proceedings); you have consented to the disclosure, including for your medical treatment; or the research information is used for other scientific research, as allowed by federal regulations protecting research participants.

Disclosure is required, however, for audits or program evaluations requested by the agency that is funding this project (the NIH, the study sponsor) or for information that may be required by the Food and Drug Administration (FDA). Any research information that is placed in your medical record would not be covered under this Certificate.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If others obtain your written consent to receive research information, then the researchers may not use the Certificate to withhold that information. Finally, you should understand that the study doctor is not prevented from taking steps, including reporting to authorities, to prevent serious harm to yourself or others.

Compensation for Participating in the Research
You will be paid up to a total of $300 if you complete all the study visits discussed above. You will be paid for the visits that you complete according to the following schedule:

- $30.00 for the completion of Visit 1
- $50.00 for the completion of Visit 2
- $30.00 for the completion of Visit 3
- $30.00 for the completion of Visit 4
- $50.00 for the completion of Visit 5
- $30.00 for the completion of Visit 6
- $30.00 for the completion of Visit 7
- $50.00 for the completion of Visit 8

If you do not complete the study, for any reason, you will be paid for each study visit you do complete. You will be paid by check upon the completion of your enrollment in the study. It may take up to 8 weeks to receive your stipend check. If you have any questions regarding your compensation for participation, please contact study staff. The findings from this research may result in the future development of products that are of commercial value. There are no plans to provide you with financial compensation of for you to share in any profits if this should occur.

Costs to Participating in the Research
All study costs include any study mediations and procedures directly related to this study will be paid for by the study. Costs for your regular medical care, which are not related to this study, will be your own responsibility. There are no costs to you for participating in this study.

Withdrawal from the Research
Your participation in this research is completely voluntary. If you chose not to participate or withdraw from the study, you will incur no penalty or loss of usual benefits. You may withdraw your consent and discontinue participation at any time without affecting your employment, job evaluations, health care or other services you may be receiving. If you choose to take part in the study, you have the right to stop at any time.

You will be informed of any significant new findings developed during the course of this research which may affect your willingness to continue participation. If you decide to stop participating in the study we encourage you to have a consultation with our study doctor.

Your participation in this research project may be terminated if any procedure is determined to be inappropriate or potentially harmful for you. The study doctors also have the right to stop your participation in the study at any time. This could be because:

1. It's in your best medical interest
2. Your condition worsened
3. New information becomes available
4. You had an unexpected reaction
5. You failed to follow study instructions
6. Or because the entire study was stopped

If you decide to leave the study or you are asked to stop participating, any data that has already been collected will be kept by the study doctors.

Authorization for Use and Disclosure of Your Protected Health Information
As part of this study, we will be collecting and sharing information about you with others. Please review this section carefully as it contains information about the federal privacy rules and the use of your information.

Protected Health Information (PHI)
By signing and dating this informed consent document, you are allowing the study doctors and other authorized personnel to use and disclose health information about you. This may include information about you that already exists such as: such as medical records, demographic information, laboratory results, etc. as well as any new information generated as part of this study through questionnaires, tests, and procedures that we may ask you to undergo. This is your Protected Health Information, or PHI.

People/Groups at HSL Who Will Use Your Protected Health Information
Your Protected Health Information, PHI, may be shared with the study listed on this consent form as well as the supporting research team (for example research assistants, statisticians, data managers, laboratory personnel, administrative assistants). Your PHI may also be shared with the Advarra IRB as it is responsible for reviewing studies for the protection of the research subjects.

People/Groups Outside of HSL with Whom Your Protected Health Information Will Be Shared
We will take care to maintain confidentiality and privacy about you and your Protected Health Information, PHI. We may share your PHI with the following groups so that they may carry out their duties related to this study:

- The sponsor of this study National Institute of Health/National Institute of Aging (for inspection and copying of records pertaining to this research) and their clinical research organizations

- Other researchers and centers that are part of this study at Marcus Institute for Aging Research
- Other collaborative organizations (e.g., the research pharmacy, clinical laboratories, etc) that are involved with this study
- Other hospitals and medical centers taking part in this study at Marcus Institute for Aging Research and research collaborators at those institutions
- Your health insurance company, for portions of the research and related care that are considered billable.
- Federal and state agencies that oversee or review research information, such as the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health, and public health and safety authorities
- Data and Safety Monitoring Board(s) that oversee this study

Those who receive your PHI may make further disclosures to others. If they do, your information may no longer be covered by the federal privacy regulations.

Why We Are Using and Sharing Your Protected Health Information
The main reason for using and sharing your Protected Health Information is to conduct and oversee the research as described in this Informed Consent Document.

No Expiration Date - Right to Withdraw Authorization
Your authorization for the use and disclosure of your Protected Health Information, PHI, in this Study shall never expire. However, you may withdraw your authorization for the use and disclosure of your PHI at any time by notifying the Principal Investigator in writing. If you do this, you will not be able to stay in this study. If you would like to withdraw your authorization, please send a letter notifying the Principal Investigator at the address listed on the first page of this form. Please be aware that the investigators in this study will not be required to destroy or retrieve any of your PHI that has already been used or disclosed before the Principal Investigator receives your letter.

Right to Access and Copy Your PHI
If you wish to review or copy your Protected Health Information, PHI, as it is made part of your medical record, you may do so after the completion or termination of the study by sending a letter to the Principal Investigator. You may not be allowed to inspect or copy your PHI until this study is completed or terminated.

Notice of Privacy Practices
In addition to signing and dating this document, you may also be asked to sign an HSL Acknowledgement Received Notice of Privacy Practices form to acknowledge that you have received the HSL Notice of Privacy Practices.

ClinicalTrials.Gov
A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Whom to Contact About This Study

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the principal investigator at the telephone number listed on the first page of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research participants. If you have any questions about your rights as a research participant, and/or concerns or complaints regarding this research study, contact:

- By mail:
  Study Subject Adviser
  Advarra IRB
  6100 Merriweather Dr., Suite 600
  Columbia, MD 21044
- or call **toll free:** 877-992-4724
- or by **email:** adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: Pro00053594.

If you agree, at the completion of this study, we would like to store the data we collect from you for possible use in future research studies. The data may be stored and used indefinitely and may be used for future studies to understand and improve function in those who fall with balance, walking or memory problems. Your data will be given a unique identification number and stored without your name or other information that could identify you. Only the investigator (or a specific person on the study staff) will have a list to know which study data are linked to which study participant, and this list will be kept confidential in a secure location. If the study doctor distributes data to other researchers, those data will be released with a unique identifier and without any way to identify you. If at any time you would like to have the data removed or deleted from storage, please let us know and the data will be transferred or destroyed according to your wishes.

(1) I agree to allow the following information and materials collected from me for this research study to be stored and used for future studies **to understand age-related disease:** Data from physical and mental assessments.
___Yes ___ No

(2) I agree to allow Dr. Lewis Lipsitz to keep my contact information and contact me in the future with information about new research opportunities. I understand that I am not obligated to participate in the future and can request to not be contacted at any time.
___Yes ___ No

Documentation of Informed Consent and Authorization:

- I have read this consent form and was given enough time to consider the decision to participate in this research.
- This research has been satisfactorily explained to me, including possible risks and benefits.
- All my questions were satisfactorily answered.
- I understand that participation in this research is voluntary and that I can withdraw at any time.
- I am signing and dating this consent form prior to participation in any research activities.
- I give permission for participation in this research and for the use of associated protected health information as described above (HIPAA).

Research Participant

_____ _____

Date (MM/DD/YEAR) Signature of Research Participant

Study Doctor or Associate's Statement, Signature & Date:

- I have fully explained the research described above, including the possible risks and benefits, to all involved parties (participant /legal guardian as applicable).
- I have answered and will answer all questions to the best of my ability.
- I will inform all involved parties of any changes (if applicable) to the research procedures or the risks and benefits during or after the course of the research.
- I have provided a copy of the consent form signed by the participant /guardian and a copy of the hospital's privacy notification (if requested).

_____ _____

Date (MM/DD/YEAR) Signature of Study Doctor or Associate