Effects of Lactoferrin on Chronic Inflammation in the Elderly (ELCIE)

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1. Abstract

Mild persistent activation of inflammatory pathways, often termed chronic inflammation (CI) is observed in up to 30% of older adults (1;2). Dozens of population studies have identified significant associations between serum-based pro-inflammatory measures and functional decline, frailty, worsening chronic illness, cognitive decline, mortality and reduced gait speed (2). Serum markers of CI such as interleukin 6 (IL6) and soluble TNF-alpha receptor 1 (sTNFR1) are increasingly recognized as pathologic and in part causal in many of age-associated processes such as sarcopenia and neurodegeneration that in turn drive functional and cognitive decline and worsening chronic disease states in older adults (3;4). The etiology of the chronic elevation of these mediators in older adults is complex and includes chronic disease states, increased free radical production, senescent cells, altered microbiome, and decreased barrier function of GI epithelium (4-6). Despite the increased understanding of etiologies and consequences of CI in older adults, few options have been tested for reducing CI and associated adverse health outcomes. This is in part because of lack of specific biological targets and because of safety concerns regarding presently utilized anti-inflammatory drugs in older adults (7). In response, this research aims to test the effects of lactoferrin (recombinant human lactoferrin {rhLF)), a known anti-inflammatory agent, on reducing low grade CI, mobility limitations, and cognitive decline in older adults.

After careful consideration of potential etiologies of CI that could be safely attenuated, and of multiple pharmaceutical and non-pharmaceutical agents that are both safe and biologically plausible to be effective against CI, our team has identified lactoferrin as an important potential treatment for CI and related declines in functional consequences in older adults. Lactoferrin is a basic glycoprotein found in most exocrine secretions and in neutrophil granules that has a pleiotropic impact on innate immune system activation (8-10). It binds to invading organisms and bacterial cellular wall products rendering them less immunogenic and easier to degrade, modulates the adaptive immune system, and it directly suppresses inflammation via NfKB mechanisms, especially in the GI tract (9-15). A prior study of oral bovine lactoferrin administration in post-menopausal women demonstrated significant reductions of CRP and IL-6 level (16). Given this background, we hypothesize that oral lactoferrin will attenuate inflammatory signaling in adults with CI. We further hypothesize that the lactoferrin induced CI attenuation will attenuate decline or facilitate measureable improvement in specific functional and cognitive measures in older adults.

To test these hypothesizes, a randomized, placebo controlled pilot trial of rhlactoferrin (rhLF) in adults over age 70 is proposed that aims to assess the efficacy of this potent anti-inflammatory nutrient on CI and restricted mobility. This study will enroll 60 patients (30 randomized to rhlactoferrin (rhLF) and 30 randomized to placebo).

At the conclusion of this pilot study, we will have determined whether recombinant human lactoferrin (rhLF) can safely reduce measures of CI in older adults, and if it has the potential to meaningfully influence important measures of physical and cognitive function known to be influenced by CI. This information will in turn be utilized to develop a more definitive clinical trial of rhlactoferrin (rhLF) for CI and adverse health outcomes in older adults.

2. Objectives

The primary objective of this study is to examine in a double blinded and randomized trial the efficacy of Recombinant Human lactoferrin (rhLF) in reducing chronic inflammation as measured by IL-6 and sTNFR1 in the bloodstream. Secondary objectives include assessing the efficacy of rhlactoferrin (rhLF) in attenuating cognitive decline as measured by the Digit Symbol Substitution Test and Trail Making Test, as well as improving physical mobility as measured by performance on 4 meter and six-minute walk tests. The tertiary objective of this study is to gather information about the tolerability of and adherence to oral rhlactoferrin (rhLF) among older adults with CI over a three-month period.

3. Background

Chronic Inflammation and Biological Mediators:

Chronic inflammation (CI) as defined by chronic elevation in serum inflammatory measures is a known risk factor for a host of adverse health outcomes in older adults (3;17;18). The etiology of CI is complex with increased chronic disease burden, fat mass, free radicals, and senescent cells, dysfunctional mitochondria, altered microbiome, and decreased GI tract barrier function all potentially contributing (19-25). Dozens of population studies have detailed significant associations between pro-inflammatory measures and functional and mobility decline, frailty, worsening chronic illness, cognitive decline, mortality and reduced gait speed (1;2;26;27;28). Although these relationships were often considered to be epidemiological phenomena rather than causal, evidence suggests that chronic exposure to some inflammatory mediators can lead directly to molecular and tissue changes that contribute to the observed adverse outcomes (29;30-34). Specifically, evidence suggests that IL-6, sTNFR1 and other molecules directly and negatively impact skeletal muscle and neurologic tissue through impairment of satellite cells, through the triggering of cell death pathways, and through other mechanisms (35-44). Figure 1 provides a conceptual overview for a biologically plausible pathway between CI and health-related declines; lactoferrin is hypothesized to impact inflammatory mediators and their downstream effects.

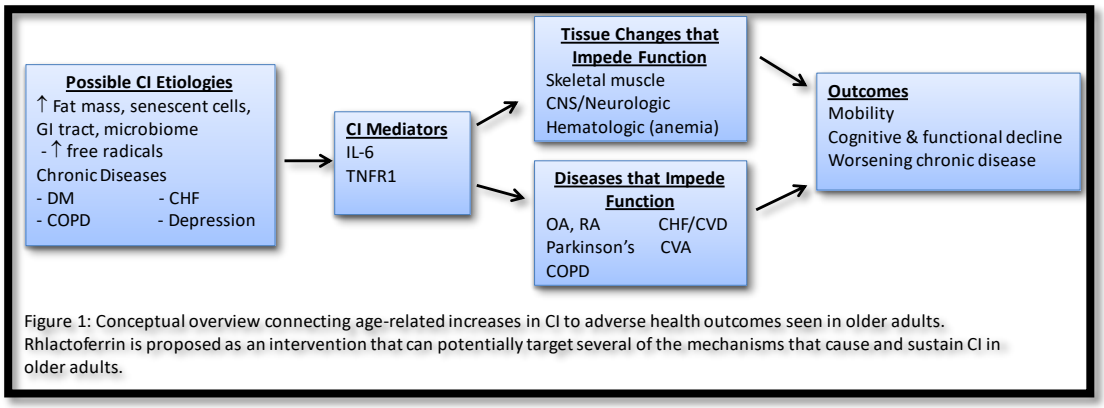

Figure 1: Conceptual overview connecting age-related increases in CI to adverse health outcomes seen in older adults. Rhlactoferrin is proposed as an intervention that can potentially target several of the mechanisms that cause and sustain CI in older adults.

Chronic Inflammation and Cognitive Decline:

A range of studies has explored how inflammation may contribute to cognitive dysfunction in an aging population (45; 46). Connections between inflammatory associated measures and cognitive declines are observed in patients with Parkinson's disease, Alzheimer's disease, and mild cognitive impairment (45). A defining feature of Alzheimer's disease is the buildup of beta-amyloid into plaques; examinations of patients with Alzheimer's disease reveals the presence several inflammatory proteins, such as cytokines and chemokines, within cerebrospinal fluid and beta-amyloid plaques (46). To target inflammation in those with neurodegenerative diseases and attenuate the effects of cognitive decline, nonsteroidal anti-

inflammatory drugs (NSAIDS) are frequently prescribed (46). As a nutrient with known-anti-inflammatory effects, it is anticipated that administration of lactoferrin will result in some improvement of cognitive function.

Diagnosing and Treating Chronic Inflammation:
To date, no clear method for diagnosing CI has been accepted. Although dozens of inflammatory measures have been used to identify associations between adverse outcomes and CI in older adults, IL6 and sTNFR1, stand out as especially relevant in part because of their known biological relevance to muscle loss (36;47-52).

Table 1: Differences in mean gait speed (top tertile of CI marker vs other), differences in rates of walking speed decline between highest / lower CI tertiles (marker*Time), and rates of gait speed decline among those with lower CI (Time), using linear mixed-effects models in CHS (n=5091)

Likelihood ratio test (LRT) statistic comparing linear mixed-effects models with and without cytokines for predicting gait speed.

Models	Estimate[a]	LRT statistic (p-value)
IIS (top tertile)	-0.047 ±0.0058	220.0 (2.8e-49)
IIS*Time	-0.005 ± 0.0009	
Time	-0.010 ± 0.0005	
IL6 (top tertile)	-0.041 ± 0.006	150.0 (4.4e-34)
IL6*Time	-0.004 ± 0.001	
Time	-0.010 ± 0.0005	
TNFR1 (top tertile)	-0.038 ± 0.0060	130.0 (2.8e-28)
TNFR1*Time	-0.005 ± 0.0010	
Time	-0.010 ± 0.0005	
ILR1a (top tertile)	-0.034± 0.0059	53.0 (2.9e-12)
ILR1a*Time	-0.0002± 0.0009	
Time	-0.011± 0.0005	
CRP (top tertile)	-0.021 ± 0.006	48.0 (4.3e-11)
CRP*Time	-0.002 ± 0.001	
Time	-0.010 ± 0.0005	

Most prior studies linking CI to adverse health in older adults have relied on single serum-based biomarkers such as IL6 or C-reactive protein (CRP). Studies have emerged that demonstrate that elevations in ≥2 inflammatory markers are more strongly associated with adverse outcomes (53-57). Approaches to aggregate markers can be categorized into "unsupervised" and "supervised", with unsupervised aggregation being a summary of markers obtained based only on their joint distribution, e.g. by z-scores, principal component analysis or exploratory factor analysis (58;60) and supervised aggregation also considering biological understanding, or externally validating response (e.g., mortality(26)) for an "optimally" predicting response. Our group has made key contributions to work on supervised aggregation of inflammatory markers; including the first study applying latent variable (LV) modeling to summarize markers in accordance with biology understanding (61). Subsequently, we demonstrated that an inflammatory index (IIS) combining serum levels of IL6 and sTNFR1 provided superior prediction of 10-year mortality in the Cardiovascular Health Study (N=5,177) (26) over many other cytokines. As rationale for the use of these measures for diagnosis of CI in this project over other markers, we performed additional analyses (table 1) using the likelihood ratio test that shows that IL-6, TNFR1, and combined measure IIS are superior predictors of gait speed declines over 10 years when compared to CRP and interleukin 1 receptor antagonist (IL1RA). The cutoff point for the study inclusion criteria for IL6 was identified based on a published threshold serum value above which adverse outcomes are much more common; the value for sTNFR1 was identified using a loess curve generated from data analyzed from the Cardiovascular Health Study (17;18;26). This background research provides strong rationale for the use of these measures to identify CI and to monitor treatment efficacy of lactoferrin on CI.

4. Study Procedures

Prescreening Contact: Subjects will be recruited from a registry of older adults who have consented to be re-contacted for studies related to aging as well as from other populations of community-dwelling older adults. Sixty individuals age 70 and over who can walk without assistance at least four meters will be studied. Study coordinators will review basic information available from the registry and make a determination on potential eligibility based on the inclusion and exclusion criteria; this information includes participants' age, ambulatory ability, and medical and neurological conditions that may exclude participation. Subjects who satisfy entry criteria will be contacted by the study coordinator or the

investigators, who will explain the study, its purpose, and its potential benefits and risks. Individuals will then be scheduled to visit Johns Hopkins Bayview for informed consent and the formal screening visit.

Screening Visit (SV): The screening visit will consist of the administration and review of the informed consent, completion of a demographic questionnaire, a medical history questionnaire, physical activity, fatigue and weight loss questionnaire, a MMSE, a physical exam, and measurements of vital signs (Height, weight, blood pressure, temperature and respiration) and two timed 4 meter walks**.** Blood will be drawn to measure CMP and CBC/w Diff; additionally a 10 cc tube of blood will be drawn, serum will be processed and stored at -80 C in the Primary Investigator's laboratory for cytokine measurement. If the cytokine levels are above the threshold for either IL-6 or TNF-R1, we will retest the prospective participant again within four weeks to confirm chronic inflammation after screening visit. This will be done at the ABT visit. (17; 18; 26). If they remain eligible by elevation of either cytokine, they will be included in the study. If eligible, the participant will be randomized to either active or placebo treatment group. After confirming eligibility the JHU Pharmacy will generate the randomization schedule, and the appropriate numbered treatment kit for that participant will be assigned.

Baseline Visit (BV): Individuals meeting eligibility criteria (described below) will be scheduled for a baseline visit. This visit will consist of a brief medical history review and blood draw, along with outcome measurements described thoroughly below. At the end of the visit, the pharmacy or site coordinator will distribute the randomized study product with instructions. A structured walking program and encouragement of physical activity for participants in all treatment arms will be included. Participants will also receive an accelerometer for home mobility measurement along with detailed instructions for use.

Follow up visit (FUV): Monthly in person visits will take place, with telephone contact every two weeks by study staff between visits to help maintain adherence and assess for adverse effects. Pill counts and side effect assessments will take place at FU1, FU2, and FU3. FU6 will include measures checked in Table 2 and described below.

Table 2

	PSC	SV	ABT	BV	FU1	FU2	FU3			FU6.
Phone Screen	X									
Medical History		X								
Brief Medical History Review				X	X	X	X			X
Informed Consent		X								
Demographics		X								
Randomization				X						
Frailty Assessment				X			X			X
Activity Assessment				X			X			X
Vital Signs (BP, HR, Hgt,Wgt. Temp, Resp.)		X	X	X	X	X	X			X
Short Physical Performance Battery				X			X			X
Side Effect Assessment					X	X	X			
4 meter walk		X		X			X			X
Six-minute walk test				X			X			X
Blood Draw		X	X	X	X		X			X
Physical Exam		X								
MMSE		X								
Cognitive measures (Trail Making Test and Digit Symbol Substitution Test)				X			X			X
Accelerometry				X			X			X
Pill Calendar			Marked Dailyto end of Month 3							
	Abbreviations: PSC: Prescreening contact; SV: Screening visit; ABT Additional Blood test (to further determine eligibility for those whose cytokine levels are above threshold); BV: Baseline visit; FU1-6: Follow up months 1-6 of pilot study									

All laboratory results will be reviewed by study physicians during the study and there will be frequent review

of adverse and/or other unexpected events. Following study protocol, all adverse events will be reported to the IRB and National Institute on Aging (NIA) as per requirements. Participants will be able to report issues at study contacts but will also be provided with a number to call ad hoc as needed if issues related to study participation arise. If participants choose to withdraw from the study, their medical care will not be affected in any way.

Measurements Performed at Visits:
Phlebotomy (primary outcome measure): Primary outcome will be serum IL-6 and sTNFR1 as measured by ELISA as previously performed in the PI's laboratory by an experienced laboratory technician. Blood will also be measured for CBC w/Diff, and CMP, these measures will be made from blood drawn at SV, ABT, BV, FU1, FU3 and FU6. Rationale for the choice of these measures are provided above in the background section.

A Physical Exam will be taken at SV. A Medical History will be taken at SV and a Brief Medical History Review at BV and all subsequent FUV. These are to assess eligibility or contraindicate the intervention, detect new conditions or complications and other safety signals, and to measure important covariates (i.e. demographics, past medical history, current activity levels, routine medication, and vitamin use).

4 meter walk: Speed of walking at usual pace over 4 meters will be measured at the SV, BV, FU3, and FU6.

Six-minute walk: This is performed at the BV, FU3, and FU6 by having the participant walk along a straight hallway for six minutes and measuring the distance walked and the sensation of leg fatigue and dyspnea. The participant is given scripted prompts at one-minute intervals, but the test is largely self-directed and self-limited.

Short Physical Performance Battery (SPPB): This is an assessment of lower extremity functioning comprised of gait speed, balance, and leg strength and is performed at the BV and FU6. As part of the SPPB, participants will complete a balance test assessing their ability to stand without assistance and a chair stand test.

Cognitive Function Measures: The Digit Symbol Substitution Test (DSST) is a sensitive measure in cognitively normal older adults. It measures attentional control and switching, and more broadly executive processes and thus is not sensitive to impairment in particular brain regions. It is a highly precise measure across the range from cognitively normal to mildly impaired older adults and takes about 90 seconds to administer (75). The DSST will be conducted at BV, FU3, and FU6. The Trail Making A and B Test measures executive functioning and task-switching, is highly sensitive to change and takes 5-10 minutes to administer (76). This test will be performed at BV, FU3, and FU6. An MMSE (a mini-mental state exam) will also be performed at the BV.

Side Effect Assessment: A Side Effect Assessment will be conducted at FU1, FU2, and FU3. The purpose of this assessment is to monitor participants' responses to lactoferrin and to assess for any adverse side effects.

Activity Assessment: Participants will answer questions about their physical activity and energy levels. This assessment is conducted at BV, FU3, and FU6.

Frailty Assessment: This assessment is completed at BV, FU3, and FU6. This assessment measures participants' walking speed and grip strength, and includes questions about weight loss.

Vital Signs: Participants' vital signs will be measured at every study visit. These measurements include height, weight, blood pressure, respiratory rate, and temperature.

Additional Physical and Functional Measurements:
Home Mobility Measurement: An Acti-Graph® Link Activity monitor will be placed on the participant's non-dominant wrist at the end of the BV. This model includes an ambient light designed to provide environmental information and a gyroscope and magnetometer to capture position and rotational data. Accelerometry counts will be measured at a sampling frequency of 80 hertz for 7 days immediately

after completing the BV, 3-month, and 6-month visits. Participants will be asked to wear the device at all times except when swimming for >30 minutes. Monitors will be mailed via pre-addressed express mail packets where all raw data will be downloaded using commercial software (ACTLIFE, v6) to derive activity data in g force and counts/min. The JHU Statistical Methods for Applications and Research in Technology ("SMART"-stats) group, developers of the "movelets" technology that enables the use of raw data (62), will use collected data to: (i) characterize cumulative daily activity, (ii) assess daily circadian patterns of activity, (iii) assess physical activity variability, (iv) model patterns of daily activity, and (iv) estimate walking speed (62, 63, 64). These measurements greatly extend what is normally available from accelerometers and will complement mobility measures by describing function enacted in daily life.

5. Inclusion/Exclusion Criteria

Inclusion: Age 70 and older; able to complete 4- meter timed walk; walking speed ≤1.0 m/sec; serum IL-6 level ≥ 2.5 pg/ml or TNFR1 level ≥1500 pg/ml. Consistent with NIH guidelines, both genders and minority persons are enrolled. Participants will be followed for 6 months to investigate the effects of the treatments on gait speed and other outcomes.

Exclusion criteria**:** Participants with IL-6 levels above 30.0 pg /ul. Daily anti-inflammatory drug use (prednisone, Advil, Aleve, Remicade, Enbrel, methotrexate, standing NSAID, aspirin greater than 325 mg per day), lower extremity mobility disability caused by Parkinson's disease, CVA with residual motor deficit, severe osteo or rheumatoid arthritis, symptomatic claudication, hospitalization within 3 months for MI, angina, infection requiring antibiotics, or joint replacement, and for other reasons that markers may be elevated such as active or chronic malignancies MMSE < 21.

6. Drugs/ Substances/ Devices

Lactoferrin is a basic glycoprotein initially identified in milk but subsequently identified in most exocrine secretions and in granules secreted from neutrophils (8). It has pleiotropic anti-inflammatory effects that range from the coating and degradation of invading organisms and their antigenic cellular components, to the sequestration of free iron needed by invading organisms to thrive, to the suppression of inflammatory (NFkB) signaling, and the modulation of the adaptive immune system (8-10;12) . A recent study that characterized a lactoferrin knock out mouse demonstrated a colonic inflammatory phenotype which suggests an important role for lactoferrin at the interface between the colon and the immune system (11). Given the evidence for altered immunogenic intestinal flora in frail older adults, and the decreasing barrier function of the aging intestinal epithelium, and the known anti-inflammatory functions of lactoferrin, the use of oral lactoferrin for CI suppression in older adults is highly biologically plausible. (13-15;65-68). Beyond this mechanistic rationale, oral lactoferrin has demonstrated to safely and significantly reduce the incidence of neonatal sepsis in prior studies (69) and post-antibiotic diarrhea in older nursing facility residents (70). In older adults, lactoferrin was well tolerated in late stage cancer patients and increased overall survival in a study that did not include inflammatory measures (71, 72). A prior study of bovine lactoferrin demonstrated significant reductions of CRP and IL-6 levels in post-menopausal women treated for 6 months with minimal or no side effects (16). Lactoferrin has previously been used as a chronic diarrhea intervention in other vulnerable populations with minimal safety concerns and few if any adverse outcomes related to lactoferrin (70;73,74).

For this study, Recombinant Human lactoferrin (rhLF) a partially iron saturated form of lactoferrin in 250 mg capsules and matching placebo capsules will be provided by Ventria Bioscience Biotech company at bulk pricing. Each capsule will contain 250 mg of rhlactoferrin (rhLF) as active ingredient and cellulose, magnesium stearate, and silicon dioxide as inert ingredients. Subjects will receive either 1500 mg of rhlactoferrin in capsule form twice a day or a placebo in exact matching capsules. Dosing will be six 250 mg capsules twice a day based on prior dosing used safely in studies of diarrhea in a nursing home population (70). This treatment will take place for approximately 3 months (87 days). Recombinant human lactoferrin (rhLF) is produced through standard methods of genetic modification and plant transformation. The rice grain in which the protein accumulates is stable and well suited as a production system Recombinant human lactoferrin has been purified from transgenic rice using standard food industry procedures and current good manufacturing practices. Each placebo capsule will contain cellulose, magnesium stearate, and silicon dioxide, manufactured in full compliance with all pharmaceutical regulation.

7. Study Statistics

Based on a two-sided two-sample t-test with a Type I error of 0.05, a sample size of 23 subjects per group (46 in total) will achieve 80% power to detect a difference of 0.86 SD or greater in logIL-6 between the treatment group and the placebo group at the end of the 6-month trial. Secondarily, we will compare the linear rate of change in logIL-6 between the treatment and the placebo groups by modeling the individual trajectories of the outcome. With 20 subjects per group, three repeated measurements of IL-6 assessed at baseline, 3, and 6 months, and a correlation of 0.54 between measurements, we will have 80% power to detect a difference of 1.3 SD units (equivalent to a cross-sectional between-group difference of 0.65SD different at 6 months) or greater in the yearly rate of change in logIL-6 between the treatment and the placebo group. The within subject between-measurement correlation of 0.54 was estimated using longitudinal data from the Women's Health and Aging Study II. Therefore, using longitudinal data, we will have adequate power to detect a difference similar to the 0.63 SD (or 2.5 pg/mL) difference observed at the end of a 6-month, randomized clinical study of a ribonuclease-enriched lactoferrin supplement in post-menopausal women (16). Given these calculations, we are aiming to recruit up to 60 individuals, 30 in each group, in order to maximize our ability to detect differences between treatment and placebo groups. This increased number beyond what are calculated here will take into account anticipated drop outs during the treatment period and leave us with an estimated 'complete completer' group of 46 total. In addition, we are estimating that we will need to have at least 250 individuals recruited into the protocol in order to identify those eligible by inflammatory mediator criteria listed above.

8. Risks

Six Minute Walk Test: This is performed by having the participant walk along a straight hallway for six minutes and measuring the distance walked and the sensation of leg fatigue and dyspnea. The participant may stop at any time if they feel uncomfortable. As with any exercise test, there is a theoretical risk that a participant could suffer cardiac risk from arrhythmia or ischemia, or orthopedic risk from falling or stumbling. Risks are minimized by conducting the test in a medically supervised environment with trained personnel.

4-meter Walk Test: This is performed by having the participant walk a distance of 4 meters while being timed. The associated risk is minimal, as the participant may stop at any time if they feel uncomfortable.

Phlebotomy: Blood draw is performed by taking blood from a vein in the forearm or antecubital fossa. This may cause pain during the insertion of the needle or slight bruising afterward. This risk is minimized by the use of disposable single needles, trained personnel, and application of pressure after the blood draw.

Questionnaires, Health History, and Physical Examination: This information is routinely collected in the process of medical care of patients. Here are not any significant physical risks from these procedures. As with all medical information, there is always the psychological distress if personal health information is not held confidential within the wishes of the participant. In order to protect participants' privacy and confidentiality, all data collected will be maintained through the use of unique study identification (ID) numbers, rather than patient names, in the study database. Blood samples will be labeled only with study ID information when transmitted or stored. No information will be disclosed in an individually identifiable form in any type of presentation or publication. Participants will be given contact information for the PI and Project Manager to answer questions or to report problems. Patients can withdraw from the study at any time without any effect on their medical care.

Data and Safety Monitoring Plan: Because this is a human intervention study, we have a Data and Safety Monitoring Board (DSMB). The DSMB has already been constituted as part of ongoing clinical studies of the Johns Hopkins Older Americans Independence Center (OAIC).

The DSMB is responsible for safeguarding the interests of participants enrolled in intervention studies, assessing the safety and efficacy of study procedures, and for monitoring the overall conduct of intervention studies supported by the Johns Hopkins OAIC.

The DSMB is an independent advisory group to the Director of NIA, and is required to provide recommendations about starting, continuing, and stopping OAIC intervention studies. Selected

observational studies may come under the purview of the DSMB if deemed by the OAIC Leadership, in consultation with NIA, to have non-negligible risks. In addition, the DSMB is asked to make recommendations, as appropriate, to the NIA about:

- Efficacy of the study intervention
- Benefit/risk ratio of procedures and participant burden
- Selection, recruitment, and retention of participants
- Adherence to protocol requirements
- Completeness, quality, and analysis of measurements
- Amendments to the study protocol and consent forms
- Performance of individual centers and core labs
- Participant safety
- Notification and referral for abnormal findings

All adverse events, regardless of severity, are monitored by the (DSMB) and reviewed by the Steering Committee during their regularly scheduled meetings. Adverse events judged by a study physician to be both serious and unexpected and related to study participation will be reported via the study form and a narrative to the IRB and NIA program official in a timely manner. An event narrative will be sent to the DSMB and to the clinical centers, with instructions for reporting to their IRB. The DSMB will decide if a teleconference is needed to discuss the event and recommend actions to the NIA. If the event is judged to be related to a study drug, the NIA will report the event to the FDA. Any unexpected fatal or life-threatening adverse events associated with the study drug will be reported to the FDA within 7 days of initial receipt; adverse events that are serious, unexpected, and associated with study drug will be reported within 15 days of initial receipt.

9. Benefits

There may be no direct benefit to participants. Study participation may involve more intensive clinical follow-up than the standard of care, and participants may benefit from this. Some participants may gain psychological satisfaction by contributing to research that may improve the outcomes for older adults with chronic inflammation.

Becoming disabled from physical or memory losses are a significant burden for older adults and to society. This project has the potential to advance knowledge toward identifying a safe and effective strategy to treat chronic inflammation that might improve both mobility and memory among older adults. We expect that results will be directly relevant to public health and clinical guidelines, and will influence policy. The risk/benefit ratio for the trials will be evaluated and every protocol will be designed so that the risks associated with participation are reasonable in relation to the important knowledge to be gained. Overall, the risks of participating in this trial are small, and the potential information gained will likely add critical knowledge that will be used to guide a definitive trial to reduce chronic inflammation and impact mobility and memory among older adults.

10. Payment and Remuneration

Participants will be reimbursed for their time, effort and related expenses (i.e. parking and transportation) in the amount of $350.00 per person. The first payment will be of $35.00 for completing the Screening Visit. The second payment will be $15.00 after completion of the ABT (additional blood draw visit). The remaining amount will be divided into three increments of $100.00 each. The third payment will be dispensed to study participants after the completion of their Baseline Visit. The next reimbursement will be given after the completion of the 3-month Follow up Visit. The final reimbursement will be given after the completion of the 6-month Follow up Visit.

11. Costs

There will be no cost to the participants for enrolling in the study as the costs associated with the study are covered by grant funds.

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