Supplements **a**nd **M**uscle Function in the **E**lderly (SAM-E)

A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Impact of a Dietary Supplement on Muscle Function in the Elderly

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3. OBJECTIVES

- **Primary Objective**

The primary objective of this study is to evaluate the effect of a dietary supplement, given as an oral tablet, on muscle performance as measured by a muscle fatigue test in elderly subjects.

- **Secondary Objective**

The secondary objectives of the study are to assess the safety and tolerability of a single oral dosage of the dietary supplement in elderly subjects. In addition, plasma concentrations of the dietary supplement following a single oral dosage in elderly subjects will be compared against historical levels determined from previous pharmacokinetic studies.

APPENDIX 1
Schedule of Events

Parameters	Screening	Baseline Visit 1[a]	Visit 2 (Day 21)	Visit 3 (Day 60)
Informed consent	X			
Pulmonary Function Tests	X			X
6 minute walk test	X			X
Inclusion and exclusion criteria	X			
Medical history	X			
Physical examination	X			X
Height and Weight	X			X
Laboratory – CBC, chemistry panel	X			X
Laboratory – serum biomarkers[b]		X	X	X
Laboratory – liver function tests		X		X
ECG	X			X
Vital Signs[c]	X	X	X	X
Study Product Dispensed		X	X	
Peak Flow Meter[d]	X	X	X	X
Review Exercise Diary		X	X	X
Quality of Life Questionnaires		X		X
Concomitant Medications	X	X	X	X
Adverse Events		X	X	X

a Should occur no more than 14 days after screening visit
b Participant should be fasting
c To include heart rate, blood pressure, temperature, and respiratory rate
d Peak flow meter dispensed at screening visit for home use; reviewed at study visits

APPENDIX 2

LABORATORY MANUAL

For Study: Supplements and Muscle Function in the Elderly (SAM-E),

A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study

Version1.1 16-SEP-2014

1. SAM-E PLASMA PHARMACOKINETICS SAMPLE PREPARATION

Refer to the table below for details of blood volume, anticoagulant, collection/handling procedures, types of tubes for plasma storage, and storage instructions.

SAM-E PK Plasma Samples	
Blood Volume	4mL
Anticoagulant	EDTA
Blood Collection Times	Per the Protocol: Baseline and at: 2, 6, and 10 hrs post-drug ingestion.
Processing of Samples	Process all blood samples within 30 minutes of collection. All blood samples are to be kept on crushed ice (do not use chilling blocks or allow to freeze) until centrifuged.
Centrifuge	Sample should be centrifuged at 2000 x g for 15 minutes in a refrigerated centrifuge (4°C).

PK Plasma Sample Shipping Instructions (QPS Lab):

Note: Aliquot 1 and Aliquot 2 of each sample set at each time point should be sent separately frozen on dry ice. Please send Aliquot 1 first. Once shipment receipt acknowledgement from ABC lab is received, then Aliquot 2 may be shipped.

!! DO NOT SHIP ON A FRIDAY!!

2. SAM-E SERUM OXIDATIVE STRESS BIOMARKERS SAMPLE PREPARATION

SAM-E Biomarker PLASMA Samples	
Blood Volume	5mL
Tube	Serum Separator (RedTop) Tube
Blood Collection Times	Per the Protocol: Baseline and at: 2, 6, and 10 hrs Post-drug ingestion.
Processing of Samples	Allow samples to clot for two hours at room temperature.
Centrifuge	Sample should be centrifuged for 20 minutes at approximately 1000 x g.
Plasma Storage Tubes	3 mL polypropylene tubes with screw caps.
Plasma Samples after Separation	2-3mL of plasma should be placed in to plasma storage tube.
Storage	Once placed in the plasma storage tube, the plasma samples should be storedat-20°Cor -80°C upright until shipped. Avoid repeated freeze/thaw cycles.

REMINDERS 1-2 DAYS BEFORE VISIT

- ☐ Call to subject:
  - Please bring in all meds
  - Questions re: mailing?
  - Eat breakfast
- ☐ Subject binder: Tag places for PI signature
- ☐ Lab slips and orders signed by PI
- ☐ Lab Requisition slips completed (subj name, DOB, U number)
- ☐ All orders completed for TRU nursing unit (Subj. name, DOB, U number on forms) & highlighted for visit
- ☐ Reminders to PIs (and IDS on Visit 2) about subject schedule
- ☐ Who will walk subject from TRU to imaging lab

VISIT 1 -- Screening Day

Be sure to have:

- ☐ Subject binder
- ☐ Traveling kit
- ☐ ID Badges
- ☐ Subject phone screen
- ☐ Copier code: 123456
- ☐ Note re: subject reimbursement info
  - SSN
  - Address
- ☐ Snack for subject

AT CRC:

- ☐ Check in with nurse for that day -- Review procedures and forms (orders, lab reqs).
- ☐ See if you can review demographics during labs.
- ☐ Greet subject
- ☐ Give water to subject
- ☐ Text PIs that subject has arrived
- ☐ Informed consent
- ☐ Subject Address and SSN
- ☐ Show signed consents to Nurse
- ☐ Register subject in Electronic Data Capture System. Need date of consent signing and DOB
- ☐ CRF demographics, inclusion/exclusion, and meds during labs draw
- ☐ Make copies of consent for subject
- ☐ Text PI with Subject Number and Blood Pressure
- ☐ Have a snack ready for subject to eat before leaving unit

What are the phases of clinical trials?

Clinical trials are usually conducted in phases that build on one another. Each phase is designed to answer certain questions. Knowing the phase of the clinical trial is important because it can give you some idea about how much is known about the treatment being studied. There are pros and cons to taking part in each phase of a clinical trial.
Although there are clinical trials for devices as well as other diseases and treatments, drugs for cancer patients are used in the examples of clinical trial phases described here.

Phase 0 clinical trials: Exploring if and how a new drug may work

The purpose of this phase is to help speed up and streamline the drug approval process. Phase 0 studies are exploratory studies that often use only a few small doses of a new drug in a few patients. The biggest difference between phase 0 and the later phases of clinical trials is that there's almost no chance the volunteer will benefit by taking part in a phase 0 trial – the benefit will be for other people in the future. Because drug doses are low, there's also less risk to the patient in phase 0 studies compared to phase I studies.

Phase 0 studies help researchers find out whether the drugs do what they're expected to do. If there are problems with the way the drug is absorbed or acts in the body, this should become clear very quickly in a phase 0 clinical trial. This process may help avoid the delay and expense of finding out years later in phase II or even phase III clinical trials that the drug doesn't act as expected too based on lab studies. Phase 0 studies aren't used widely, and there are some drugs for which they wouldn't be helpful. Phase 0 studies are very small, often with fewer than 15 people, and the drug is given only for a short time. They're not a required part of testing a new drug.

Phase I clinical trials: Is the treatment safe?

Phase I studies of a new drug are usually the first that involve people. The main reason for doing phase I studies is to find the highest dose of the new treatment that can be given safely without serious side effects. Although the treatment has been tested in lab and animal studies, the side effects in people can't always be predicted. These studies also help to decide on the best way to give the new treatment.

Phase II clinical trials: Does the treatment work?

If a new treatment is found to be reasonably safe in phase I clinical trials, it can then be tested in a phase II clinical trial to find out if it works. The type of benefit or response the doctors look for depends on the goal of the treatment. It may mean the cancer shrinks or disappears. Or it might mean there's an extended period of time where the cancer doesn't get any bigger, or there's a longer time before the cancer comes back. In some studies, the benefit may be an improved quality of life. Many studies look to see if people getting the new treatment live longer than they would have been expected to without the treatment.

Phase III clinical trials: Is it better than what's already available?

Treatments that have been shown to work in phase II studies usually must succeed in one more phase of testing before they're approved for general use. Phase III clinical trials compare the safety and effectiveness of the new treatment against the current standard treatment. Because doctors do not yet know which treatment is better, study participants are often picked at random (called *randomized*) to get either the standard treatment or the new treatment. When possible, neither the doctor nor the patient knows which of the treatments the patient is getting. This type of study is called a *double-blind study*. Randomization and blinding are discussed in more detail later.

Submission for FDA approval: New drug application (NDA)

In the United States, when phase III clinical trials (or sometimes phase II studies) show a new drug is more effective and/or safer than the current standard treatment, a new drug application (NDA) is submitted to the Food and Drug Administration (FDA) for approval. The FDA then reviews the results from the clinical trials and other relevant information. Based on the review, the FDA decides whether to approve the treatment for use in patients with the type of illness the drug was tested on. If approved, the new treatment often becomes a standard of care, and newer drugs must often be tested against it before being approved. If the FDA feels that more evidence is needed to show that the new treatment's benefits outweigh its risks, it may ask for more information or even require that more studies be done.

Phase IV clinical trials: What else do we need to know?

Drugs approved by the FDA are often watched over a long period of time in phase IV studies. Even after testing a new medicine on thousands of people, the full effects of the treatment may not be known. Some questions may still need to be answered. For example, a drug may get FDA approval because it was shown to reduce the risk of cancer coming back after treatment. But does this mean that those who get it are more likely to live longer? Are there rare side effects that haven't been seen yet, or side effects that only show up after a person has taken the drug for a long time? These types of questions may take many more years to answer, and are often addressed in phase IV clinical trials.

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Small Group Activity

1. What section of the protocol is the most important? Why?

2. Do you need to know the background/science of the study? Why or why not?

3. Why do we care about footnotes on the schedule of events?
    a. Are there any that impact your study visit? How do they impact the visit?

4. Name one piece of information from the lab manual that will impact the coordination of study visits.
    a. How will this impact the visits?