

**Supplementary Table S1. Selected Translational Geroscience Network Clinical Trials of Senolytics**

<b>Trial</b>	<b>Senolytic Agent</b>	<b>Notes</b>	<b>Status</b>	<b>Funding Agency</b>	<b>Site(s)</b>	<b>ClinicalTrials.gov Identifier (NCT)</b>
AFFIRM: Alleviation by Fisetin of Frailty, Inflammation, and Related Measures in Older Women	Fisetin	Phase 2 Double-Blind, Placebo-Controlled. Gait Speed <0.6 M/sec	Recruiting	Benefactor	Mayo	03430037
AFFIRM-LITE: Alleviation by Fisetin of Frailty, Inflammation, and Related Measures in Older Adults	Fisetin	Phase 2 Double-Blind, Placebo-Controlled. Gait Speed ≥0.6 M/sec	Recruiting	Benefactor	Mayo	03675724
ALSENLITE: An Open-Label, Pilot Study of Senolytics for Alzheimer Disease	D+Q	Target Engagement; Double-Blind, Placebo-Controlled	Active, Not Yet Recruiting	Alzheimer's Association	Mayo	04785300
Pilot Study to Investigate the Safety and Feasibility of Senolytic Therapy to Modulate Progression of Alzheimer's Disease (SToMP-AD)	D+Q	Open Label Pilot Phase	Recruiting	UTHSCSA Internal Funding	UTHSCSA	04063124
Senolytic Therapy to Modulate the Progression of Alzheimer's Disease (SToMP-AD)	D+Q	Cognitive Function; Double-Blind, Placebo-Controlled	Active, Not Yet Recruiting	Alzheimer's Drug Discovery Foundation	Mayo, UTHSCSA, Wake Forest	04685590
Senescence in Chronic Kidney Disease	D+Q	Open Label	Recruiting; Pilot Study Published	Benefactor	Mayo	02848131
Inflammation and Stem Cells in Diabetic and Chronic Kidney Disease	Fisetin	Double-Blind, Placebo-Controlled	Recruiting	Benefactor	Mayo	03325322
Hematopoietic Stem Cell Transplant Survivors Study (HTSS)	D+Q	Randomized; Parallel Assignment; Open-Label	Recruiting	Benefactor	Mayo	02652052
Senolytics to Improve Cognition and Mobility in Older Adults at Risk of Alzheimer's	D+Q	Single Arm, Open Label, Pre-Post Pilot Study	Not Yet Recruiting	NIH	Harvard (Hebrew Rehabilitation Center)	Pending

Disease						
SENSURV: An Open-Label Intervention Trial to Reduce Senescence and Improve Frailty in Adult Survivors of Childhood Cancer	Fisetin; D+Q	Randomized, Open-Label	Active, Not Yet Recruiting	NIH	St. Jude (1° Site); Mayo (Assays)	04733534
IPF: Trial of Senolytics in Idiopathic Pulmonary Fibrosis	D+Q	Double-Blind, Placebo-Controlled	Planned (Open-Label Pilot Study Published)	Pending	UTHSCSA; Wake Forest; Mayo	02874989 (Pilot Phase)
Targeting Cellular Senescence with Senolytics to Improve Skeletal Health in Older Humans	Fisetin; D+Q	Randomized; Parallel Assignment; Open Label	Recruiting	NIH	Mayo	04313634
Senolytic Drugs Attenuate Osteoarthritis-Related Articular Cartilage Degeneration: A Clinical Trial	Fisetin	Double-Blind, Placebo-Controlled	Recruiting	Office of Naval Research	Steadman Clinic (1° Site); Mayo (Assays)	04210986
COVID-FIS, A Study of Fisetin for Skilled Nursing Facility Residents with COVID-19	Fisetin	Double-Blind, Placebo-Controlled	Recruiting	NIH	Mayo	04537299
COVID-FISETIN: Pilot in SARS-CoV-2 of Fisetin to Alleviate Dysfunction and Inflammation	Fisetin	Double-Blind, Placebo-Controlled	Enrolling by Invitation	Benefactor	Mayo	04476953
COVFIS-HOME: COVID-19 Pilot Study of Fisetin to Alleviate Dysfunction and Disease Complications	Fisetin	Double-Blind, Placebo-Controlled	Active, Not Yet Recruiting	Benefactor	Mayo	04771611

**Abbreviations:** St. Jude (St. Jude Children's Research Hospital); UTHSCSA (University of Texas Health Sciences Center at San Antonio); Wake Forest (Wake Forest University)

## Supplementary Table S2. Excluded Medications and Dosing Modifications

### Cardiac:

- Digoxin
- Flecainide
- Amiodarone

### Psychiatric:

- Duloxetine (Cymbalta)
- Lithium
- Clozapine (Clozaril)
- Thioridazine (Mellaril or Melleril)

### Neurologic:

- Carbamazepine (Tegretol)
- Phenobarbital (Luminal and Solfoton)
- Phenytoin (Dilantin, Phenytoin Sodium, Phenytek)
- Fosphenytoin (Cerebyx)
- Riluzole (Rilutek; used to treat amyotrophic lateral sclerosis)

### Antimicrobial/fungal:

- Aminoglycosides (*e.g.*, amikacin, gentamicin, kanamycin, neomycin, netilmicin, paromomycin, streptomycin, tobramycin)
- Azole antifungals (fluconazole, miconazole, voriconazole) – (if cannot be discontinued, levels must be subtherapeutic or therapeutic)
- Macrolides (clarithromycin)
- Antivirals (nelfinavir, indinavir, saquinavir)

### Oral hypoglycemic/Anti-Diabetes drugs:

- Glimepiride (Amaryl)
- Glyburide (DiaBeta, Glynase PresTab, Micronase)

### Anticoagulants/ Antiplatelet:

- Warfarin
- Full dose aspirin

### Others:

- Cyclosporine
- Methotrexate
- Nitroglycerin
- St. John's Wort
- Theophylline
- Tyrosine Kinase Inhibitors
- Tizanidine (Zanaflex)
- Tacrine
- Diclofenac

**Supplementary Table S3. Tyrosine Kinase Inhibitor List (CYP2C8)**

afatinib	crizotinib	imatinib	ponatinib	Tarceva	Xalkori
axitinib	dasatinib	Imbruvica	regorafenib	Tasigna	Zaltrap
Bosulif	erlotinib	Inlyta	sorafenib	Tivopath	ziv-aflibercept
bosutinib	Gilotrif	lapatinib	Sprycel	tivozanib	
cabozantinib	Gleevec	Nexavar	Stivarga	Tykerb	
Caprelsa	ibrutinib	nilotinib	sunitinib	vandetanib	
Cometriq	Iclusig	pazopanib	Sutent	Votrient	

**Supplementary Table S4. Schedule of Events**

Procedures	Screening	Baseline / Treatment	Treatment	Follow-up	Long-Term Follow-up		
	-2 to 0	0 & 1	8 & 9	14 ( $\pm 2$ days)	30 (-2 to +7 days)	90 ( $\pm 14$ days)	180 ( $\pm 14$ days)
Verify Inclusion/Exclusion Criteria	X	X	X				
Informed Consent	X						
Demographics & Medical History	X						
Randomization		X					
IP Administration		X	X				
WHO Ordinal Scale	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X
MDS (as available)		X			X	X	X
Chest Imaging	X	X	X	X	X	X	X
SARS-CoV-2	X						
Influenza Rapid Test	X						
Safety Labs	X			X		X	X
Research Labs (blood and urine) & Biospecimens for Future Research Labs				X			

\*Items in green are mandatory.

### Supplementary Table S5. Primary Outcome Scale

7-point scale for SNF SARS-CoV-2 severity adapted from the WHO Ordinal Scale for Clinical Improvement of SARS-CoV-2\*:

1. Not hospitalized nor on additional oxygen (compared to baseline), at baseline level of function (as assessed by activities of daily living).
2. Not hospitalized nor on additional oxygen, but below previous level of function.
3. Hospitalized or moved to a more intensive unit within the SNF because of additional dysfunction (not simply because of positivity), but not requiring additional oxygen nor placed on an antiviral drug for worsening SARS-CoV-2 symptoms.
4. Hospitalized or moved to a more intensive unit within the SNF and/or requiring additional oxygen (vs. baseline) and/ or placed on an antiviral drug for worsening SARS-CoV-2 symptoms.
5. Requiring additional oxygen by ECMO or ventilator.
6. Transferred to palliative care to provide end-of-life care, including palliative care within the SNF.
7. Death.

\*The WHO Ordinal Scale for Clinical Improvement of SARS-CoV-2 is scored from 0 to 8 with 0 = no evidence of infection to 8 = death (WHO R&D Blueprint Novel Coronavirus: <https://apps.who.int/iris/handle/10665/330695>). Our adapted scale does not include scores 0 or 1, since no subjects in COVID-FIS will meet these criteria (*e.g.*, all subjects have proven SARS-CoV-2 infection, so none have “no infection”).

### **Supplementary Table S6. Points to Consider for Inclusion in Memoranda of Understanding with SNFs**

- Memoranda of Understanding (MOU) are utilized to establish a long-term collaboration encompassing educational, research, innovation, and administration activities between the institution and SNF.
- An MOU may also be referred to as a partnership agreement, collaboration agreement, or research agreement. Regardless of name, all are intended to establish the legal requirements the parties will abide by.
- The MOU will include an Exhibit outlining the project-specific details and expectations the parties are agreeing to. The Exhibit can be created in partnership with SNF leaders to tailor the project to the specific needs of the parties.
- The MOU should include a statement that both parties will protect the other's confidential information.
- The MOU should include a statement that both parties will comply with and conduct all activities under the MOU in compliance with all applicable laws, regulations, guidelines and statutes.
- The MOU should include a statement regarding duration of validity (*e.g.*, for two years after the effective date.)
- The MOU should include statements about conditions under which the MOU can be terminated or extended.
- The MOU should include a statement that each party acts as an independent entity and that it is not intended by the parties to create a formal partnership or business organization and that each party can enter into cooperative arrangements with other parties to suit their organizational needs.

**Supplementary Table S7. Frequently Asked Questions (FAQ) and Scripting for SNF Medical Director\***

<p>Script for introducing trial to facility leadership:</p>	<p>We have the opportunity to participate in a clinical trial that is being conducted by world-renowned experts at the Mayo Clinic to study how a naturally occurring substance with anti-aging and anti-inflammatory properties called Fisetin may improve COVID-19 outcomes. Historically, SNF residents have been almost universally excluded from clinical trials, which has left them unable to fully benefit from medical advances. Facilitating participation of our residents in this trial has the potential to provide direct benefit for them and improve healthcare for all older adults in the long run. The study team is focused on making this process as easy as possible for SNFs, with essentially no extra work required by staff when a SNF resident is participating in the trial. I think this is an exciting opportunity and am strongly supportive of patients in our facility being afforded the chance to participate. What are your thoughts? Do you have questions about the trial that I can help answer?</p>
<p>What is Fisetin?</p>	<p>Fisetin is a substance with anti-aging and anti-inflammatory properties that is found naturally in strawberries as well as other fruits, vegetables, nuts, and wine. The dose of Fisetin being studied in this trial is much higher than that occurring naturally in typical portions of these foods. Fisetin has shown benefit against viral infection in human cells, tissues, and in an animal model of infection. It is administered orally as a pill or powder. Because it has little taste or smell, it can be mixed in foods such as apple sauce, pudding, or yogurt, or in chilled or room temperature beverages.</p>
<p>Why is this trial being conducted?</p>	<p>COVID-19 has had a profound and disproportionate negative impact on older adults, particularly those residing in SNF and other long-term care facilities. Though vaccination has improved the situation to some extent, COVID-19 will not likely disappear. Effective treatments that minimize morbidity and mortality in older adults in SNF are urgently needed. Fisetin has potential to be one of those.</p>
<p>Why is it being done in skilled nursing facilities (SNF)?</p>	<p>Historically, SNF residents have been excluded from participation in clinical trials. Despite being a group that would potentially benefit the most from interventions targeting aging mechanisms, age-related diseases, and susceptibility to infections, these individuals are routinely overlooked. Now that many new drugs are under development that could directly impact debilitating age-related conditions, including COVID-19 infection, Mayo Clinic and the Kogod Center on Aging are seeking to establish a national research network to address these opportunities in this most vulnerable population.</p>
<p>Who is conducting and paying for the trial?</p>	<p>The clinical trial is funded through a National Institute on Aging (NIA)/National Institutes of Health (NIH) grant program, “NIA Multi-site COVID-19 Related Clinical Trial Implementation Grant on Aging-Related Topics in at-risk Older Adult Populations”. The study is approved through the NIA and the Mayo Institutional Review Board (IRB) to optimize patient safety. The study participants are SNF residents, not the SNF itself.</p>



How will this benefit our residents?	If Fisetin is indeed effective in treating COVID-19 infection, those who receive the drug may have direct, immediate benefit from its use in the form of reduced morbidity and mortality due to COVID-19. In a larger sense, participation in clinical trials of this nature will help geriatricians and geroscientists develop and hone strategies to treat age-related diseases, and this has the potential to have profound positive impact for all older adults in the coming years and decades.
What extra work will be required by our staff as part of the trial?	We recognize that your staff are very busy and we have made it a priority to minimize impact on staff when an SNF resident chooses to participate in the trial. No extra staff work should be required.
What are the safety concerns with the trial drug (Fisetin)?	We have not encountered any serious or severe side-effects of the medication in our ongoing clinical trials that have involved 60 subjects so far.
How do we get the drug? How about orders to give the drug?	The medication or placebo will be provided and delivered by the Mayo research pharmacy. It will be secured on site at your facility using storage provided by the research team. You (the medical director) will provide the order to administer the drug or placebo to trial participants.
Who communicates with the patient and family about the trial?	This will all be done by Mayo Clinic research coordinators and providers. There are no expectations for your staff to be involved.
What follow-up happens after the drug is given?	Follow-up is most intense during the first 14 days after the drug is initially administered and includes several visits from a research team nurse as well as two urine/blood collections. Beyond that, follow-up continues sporadically for 6 months, with visits and specimen collections at 90 and 180 days.
If blood draws are part of the follow-up, how are those done since Mayo outcall phlebotomists will not draw blood on COVID-positive patients?	The research team will perform these collections and will work individually with facilities to develop a plan to do this safely and efficiently.
If this substance (Fisetin) is so beneficial, occurs naturally in strawberries, and is available to purchase on Amazon and other sites, why are we just studying it now?	While the benefits of Fisetin have been suspected for several years, the process of studying a new drug initially in cells and animal models, demonstrating success in blunting disease, then designing and gaining approval for clinical trials to test the drug in humans is a time-consuming yet essential process.

\* This sample is for SNFs near Mayo Clinic. Similar forms will be used for SNFs near other Translational Geroscience Network institutions (Harvard [Hebrew SeniorLife], Johns Hopkins, and Wake Forest Universities, Universities of Connecticut, Michigan, and Minnesota, and University of Texas Health Sciences Center at San Antonio).

## Supplementary Table S8. Additional References

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