COVID-FIS: A Phase 2 Placebo-Controlled Pilot Study in COVID-19 of Fisetin

to Alleviate Dysfunction and Excessive Inflammatory Response in Older Adults

in Nursing Homes

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MAYO CLINIC

Name and Clinic Number
Protocol #: 20-008867 **Subject ID:** **Version #:** **Version Date:**

Approval Date: **April 4, 2024**
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RESEARCH PARTICIPANT CONSENT AND PRIVACY AUTHORIZATION FORM

Study Title: COVID-FIS: A Phase 2 Placebo-Controlled Pilot Study in COVID-19 of Fisetin to Alleviate Dysfunction and Excessive Inflammatory Response in Older Adults in Nursing Homes

IRB#: 20-008867

Principal Investigator: Dr. James L. Kirkland and Colleagues

Key Study Information

This section provides a brief summary of the study. It is important for you to understand why the research is being done and what it will involve before you decide. **Please take the time to read the entire consent form carefully and talk to a member of the research team before making your decision.** You should not sign this form if you have any questions that have not been answered.	
It's Your Choice	This is a research study. Being in this research study is your choice; you do not have to participate. If you decide to join, you can still stop at any time. You should only participate if you want to do so. You will not lose any services, benefits or rights you would normally have if you choose not to take part.
Research Purpose	The purpose of this research is to determine if Fisetin treatment can prevent progression of COVID-19 infection severity and deterioration of physical function (frailty) of nursing home residents and to evaluate the safety, effectiveness, and tolerability of Fisetin in this patient population. Fisetin is a naturally occurring substance found in strawberries and other foods, but at lower doses than used in this study. The study drug Fisetin used in the study is not approved by the U.S. Food and Drug Administration (FDA) for the uses being tested in this study. The uses in this study are considered "investigational."

	However, the FDA has allowed the use of Fisetin in this research study. 0You are being asked to take part in this research study because you: have tested positive for the COVID-19 infection, are at least 65 years of age and are a nursing home resident.
What's Involved	To see if you can be in the study, a number of screening tests and procedures are required. If you are eligible, this study will take about 6 months to complete. This study uses a placebo. A placebo looks exactly like the study drug, but it contains no active ingredient. We use placebos in research studies to learn if the effects seen in research participants are truly from the study drug. If you are eligible to participate, you will be randomized (by chance, like flipping a coin) to receive either Fisetin or placebo. Study participation involves blood and urine testing and monitoring of vital signs and oxygen needs.
Key Information	Some of the risks associated with this study include possible side effects from study medication and possible infection, bruising, or swelling from blood draw. The risks associated with study participation are completely described later in this form, be sure to review them carefully. There may or may not be any direct benefit to participating in this study; it is being done for research purposes. If you decide not to take part in this study, you will still be able to receive medical care. The research team will discuss other treatment options with you.
Learn More	If you are interested in learning more about this study, read the rest of this form carefully. The information in this form will help you decide if you want to participate in this research or not. A member of our research team will talk with you about taking part in this study before you sign this form. If you have questions at any time, please ask us.

Making Your Decision

Taking part in research is your decision. Take your time to decide. Feel free to discuss the study with your family, friends, and healthcare provider before you make your decision. Taking part in this study is completely voluntary and you do not have to participate.

If you decide to take part in this research study, you will sign this consent form to show that you want to take part. We will give you either a printed or electronic copy of this form to keep. A copy of this form will be put in your medical record.

If you are signing this consent form for someone else, "you" in the consent form refers to the participant.

For purposes of this form, Mayo Clinic refers to Mayo Clinic in Arizona, Florida and Rochester, Minnesota; Mayo Clinic Health System; and all owned and affiliated clinics, hospitals, and entities.

Contact Information

If you have questions about …	You can contact …
▪ Study tests and procedures ▪ Materials you receive ▪ Research-related appointments ▪ Research-related concern or complaint ▪ Research-related injuries or emergencies ▪ Withdrawing from the research study	**Principal Investigator:** Dr. James Kirkland **Phone:** (507) 266-9151 **Study Team Contact:** Ashley Lind **Phone:** (507) 293-4487 **Institution Name and Address:** Mayo Clinic 200 First Street SW Rochester, MN 55905
▪ Rights of a research participant	**Mayo Clinic Institutional Review Board (IRB)** **Phone:** (507) 266-4000 **Toll-Free:** (866) 273-4681
▪ Rights of a research participant ▪ Any research-related concern or complaint ▪ Use of your Protected Health Information ▪ Stopping your authorization to use your Protected Health Information ▪ Withdrawing from the research study	**Research Participant Advocate (RPA)** **(The RPA is independent of the Study Team)** **Phone:** (507) 266-9372 **Toll-Free:** (866) 273-4681 **E-mail:** researchparticipantadvocate@mayo.edu
▪ Billing or insurance related to this research study	**Patient Account Services** **Toll-Free:** (844) 217-9591

Other Information:

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.

Why are you being asked to take part in this research study?

You are being asked to take part in this research study because you: have tested positive for the COVID-19 infection, are at least 65 years of age and are a nursing home resident.

Eligible subjects will be assigned randomly (by chance like flipping a coin) to receive either Fisetin (the treatment drug) or placebo (which looks exactly like the treatment drug but contains no active ingredient). You will have a 50% chance of receiving Fisetin.

The plan is to have about 150 people take part in this study.

Why is this research study being done?

Some people who become sick with COVID-19 develop a very serious disease.

The purpose of this research is to determine if Fisetin can assist in preventing progression of COVID-19 infection severity and deterioration of physical function (frailty) of nursing home residents and to evaluate the safety, effectiveness, and tolerability of Fisetin in this patient population.

Senescent cells accumulate with aging and in younger people, in tissues affected by chronic diseases, such as fat tissue in obesity and diabetes, in the brain in Alzheimer's disease, in bones in osteoporosis, in joints in osteoarthritis, in the lungs from smoking, and in blood vessels and the heart in cardiovascular diseases, atherosclerosis, and high blood pressure. Some senescent cells release factors that damage the tissues around them and at a distance, as well as interfering with the immune system.

Fisetin selectively decreases the burden of senescent cells. It is a "senolytic" drug. It temporarily disables the factors in senescent cells that prevent them from dying due to the factors that they release to kill cells and damage tissues around them: it effectively allows senescent cells to kill themselves within a few hours.

In this study, you will get either Fisetin or placebo.

The study drug Fisetin used in the study is not approved by the U.S. Food and Drug Administration (FDA) for the uses being tested in this study. The uses in this study are considered "investigational." However, the FDA has allowed the use of Fisetin in this research study.

Information you should know

Who is Funding the Study?

This study is being funded by the National Institute on Aging.

Information Regarding Conflict of Interest:

This research has been reviewed by the Mayo Clinic Conflict of Interest Review Board and is being conducted in compliance with Mayo Clinic Conflict of Interest policies. One or more of the investigators associated with this project and Mayo Clinic have a financial interest in technology used in the research and that the investigator(s) and Mayo Clinic may stand to gain financially from the successful outcome of the research. Both the Mayo Clinic Conflict of Interest Review Board and the Institutional Review Board have reviewed the financial interest for one or more of the investigators and/or Mayo Clinic related to this research and they have determined that this financial interest poses no additional significant risk to the welfare of participants in this research project or to the integrity of the research.

Additional information is available to any interested study participant regarding the details of this financial interest and how it is being managed by contacting the study coordinator or the Office of Conflict of Interest Review at 507-284-0075.

Your healthcare provider may be referring you to this research study. If your healthcare provider is also an investigator on this study, there is the chance that his or her responsibilities for the study could influence his or her recommendation for your participation. If you prefer, your healthcare provider will be happy to refer you to another investigator on the research study team for you to decide if you want to participate in the study and to see you for the research study activities while you are in the study.

How long will you be in this research study?

To see if you can be in the study, a number of screening tests and procedures are required. If you are eligible, this study will take about 6 months to complete.

Efforts will be made to make this study as minimally disruptive as possible. For your safety and convenience, study staff will obtain a majority of the data for this study by communicating with nursing home staff and obtaining relevant information from your nursing home records and/or electronic medical record. Ideally, you will be able to complete the study without having to travel to the hospital or clinic for any research visits.

What will happen to you while you are in this research study?

If you are eligible and decide to take part, we will assign you by chance (like flipping a coin) to either the Fisetin (treatment) group or to the placebo group. You and the Principal Investigator can't choose your study group. You will have an equal chance of being assigned to one or the other. Whichever happens, you will still get standard of care treatment.

Study drug (Fisetin or placebo) will be given on two consecutive days twice, on Days 0 and 1 and then again on Days 8 and 9. Each dosing will take 10 to 30 minutes to complete, if possible. The study drug may be given orally or as NG or D (feeding) tube treatments.

This study uses a placebo. A placebo looks exactly like the study drug, but it contains no active ingredient. We use placebos in research studies to learn if the effects seen in research participants are truly from the study drug.

During the Screening Visit, we will do some tests and procedures to see if you are eligible to take part in this research study. The study investigators will review the results of these tests and procedures. If you aren't eligible, study staff will tell you why. At this visit we will:

Screening Visit will consist of the following:

- Informed consent
- Review of your current medications.
- Review of your medical history and allergies, including the following (e.g., date of first COVID-19 symptoms, overall symptoms, exposure source, demographics, baseline characteristics). This information may be collected from your electronic medical record and/or nursing home records

- Eligibility confirmation.
- Blood collection.
- COVID-19 test (if it has been over 10 days since your last COVID-19 test).
- Influenza test (if you have not had one completed in the past 10 days, if applicable).
- RSV test (if you have not had one completed in the past 10 days, if applicable).
- Collection of relevant information from your electronic medical record and/or nursing home records (physical examination results, blood pressures, temperatures, weight, height, respiratory rate, oxygen saturation (SpO_2), etc.).

Baseline (Days 0 and 1) will consist of the following**:**

- Eligibility confirmation.
- Collection of relevant information from your electronic medical record and/or nursing home records (physical examination results, blood pressures, temperatures, weight, respiratory rate, oxygen saturation (SpO_2), etc.).
- Review of any changes in your health or medications.
- Randomization and administration of study drug (Fisetin or placebo) on Days 0 and 1.

Days 8 and 9 will consist of the following**:**

- Confirm eligibility to re-dose.
- Collection of relevant information from your electronic medical record and/or nursing home records (physical examination results, blood pressures, temperatures, weight, respiratory rate, oxygen saturation (SpO_2), etc.).
- Assessment of Clinical Improvement
- Review of any changes in your health or medications.
- Administration of study drug on Day 8 and Day 9.

Day 14 will consist of the following**:**

- Collection of relevant information from your electronic medical record and/or nursing home records (physical examination results, blood pressures, temperatures, weight, respiratory rate, oxygen saturation (SpO_2), etc.).
- Assessment of Clinical Improvement
- Review of any changes in your health or medications.
- If possible, blood collection including collection of sample for future research.
- If possible, urine collection including collection of sample for future research.

Day 30 (-2 to +7 days) will consist of the following**:**

- Collection of relevant information from your electronic medical record and/or nursing home records (physical examination results, blood pressures, temperatures, weight, respiratory rate, oxygen saturation (SpO_2), etc.).

- Assessment of Clinical Improvement
- Review of any changes in your health or medications.

Days 90 and 180 (± 14 days) will consist of the following**:**

- Collection of relevant information from your electronic medical record and/or nursing home records (physical examination results, blood pressures, temperatures, weight, respiratory rate, oxygen saturation (SpO_2), etc.).
- Assessment of Clinical Improvement
- Review of any changes in your health or medications.
- If possible, blood collection.
- If possible, urine collection.

If you have any chest imaging (e.g., chest x-rays) done as part of your regular care the results will be recorded for the research study.

Tests done only for research purposes are not meant to provide clinical information or help care for you. The results are only important for research. Therefore, the results of tests done with your information and samples will not be provided to you. In the rare event that a finding might affect the health of you or your family, we will contact you and you can choose whether to receive or refuse the information. If you decide to follow up and further medical testing or care is needed, the costs will be billed to you or your insurance.

What are the possible risks or discomforts from being in this research study?

RISKS OF TAKING FISETIN

As with any medication, allergic reactions are possible. In addition, you may have side effects while on this study. A side effect is an undesirable experience that may or may not be related to Fisetin, or any of the tests performed in the study.

Fisetin was shown to cause DNA damage to human cells in the test tube. The relevance of this result to the study in which you are participating is unknown.

There are possible drug interactions and behavior activities (caffeine use, tobacco or nicotine use) for which we established exclusion criteria or modification plans to minimize risks.

Your 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.

The current supply of the study drug may contain lower than anticipated amounts of Fisetin. In addition, the placebo contains trace amounts of Fisetin. It is not felt that this is a safety concern for study subjects and will not impact the study.

BLOOD DRAW: The risks of drawing blood include pain, bruising, lightheadedness, fainting, or rarely, infection at the site of the needle stick.

CONFIDENTIALITY: As with all research, there is a chance that confidentiality could be compromised; however, we take precautions to minimize this risk.

Talk to the researcher and/or your healthcare provider about side effects and ask any other questions.

Are there reasons you might leave this research study early?

Taking part in this research study is voluntary. You may decide to stop at any time. You should tell the Principal Investigator if you decide to stop and you will be advised whether any additional tests may need to be done for your safety.

In addition, the Principal Investigator or Mayo Clinic may stop you from taking part in this study at any time:

- If it is in your best clinical interest,
- If you don't follow the study procedures,
- If the study is stopped

If you leave this research study early, or are withdrawn from the study, no more information about you will be collected; however, information already collected about you in the study may continue to be used.

We will tell you about any new information that may affect your willingness to stay in the research study.

What if you are injured from your participation in this research study?

Where to get help:

If you think you have suffered a research-related injury, you should promptly notify the Principal Investigator listed in the Contact Information at the beginning of this form. Mayo Clinic will offer care for research-related injuries, including first aid, emergency treatment and follow-up care as needed.

Who will pay for the treatment of research related injuries?

Care for such research-related injuries will be billed in the ordinary manner, to you or your insurance. Treatment costs for research-related injuries not covered by your insurance will be paid by Mayo Clinic.

What are the possible benefits from being in this research study?

This study may not make your health better. Others with COVID-19 infections may benefit in the future from what learned in this study. It is for the benefit of research that we are doing this study.

What alternative do you have if you choose not to participate in this research study?

You don't have to be in this study to receive treatment for your condition. Your other choices may include antivirals, immune modulator drugs, glucocorticoids, hydroxychloroquine, azithromycin, remdesivir and/or convalescent plasma. Note that receiving the institutional standard of care treatment for COVID-19 with these medications does not exclude you from participating in this study. Also, note that Fisetin can be obtained outside of this protocol. Talk to the Principal Investigator or your doctor if you have any questions about any of these treatments.

What tests or procedures will you need to pay for if you take part in this research study?

You won't need to pay for tests and procedures that are done just for this research study. These tests and procedures are:

- Research blood draws and tests
- Research urine tests
- SARS-CoV-2 test (if applicable)
- Influenza rapid test (if applicable)
- RSV rapid test (if applicable)
- Study drugs

However, you and/or your insurance will need to pay for all other tests and procedures that you would have as part of your standard clinical care, including co-payments and deductibles.

If you have billing or insurance questions call Patient Account Services at the telephone number provided in the Contact Information section of this form.

Will you be paid for taking part in this research study?

You will not be paid for participating in this study.

There is a very small chance that some commercial value may result from the use of your sample. This could include new products like a drug or a test to diagnose a disease. If that happens, you will not be offered a share in any profits.

Will your information or samples be used for future research?

Identifiable information such as your name, Mayo Clinic number, or date of birth may be removed from your information or samples collected in this study, allowing the information or samples to be used for future research or shared with other researchers without your additional informed consent.

How will your privacy and the confidentiality of your records be protected?

Mayo Clinic is committed to protecting the confidentiality of information obtained about you in connection with this research study. Your name will not be identified with your study data, results, or samples. A unique subject identification number assigned to you will be used as a code for this study. Data stored on a computer will be password-protected.

During this research, information about your health will be collected. Under Federal law called the Privacy Rule, health information is private. However, there are exceptions to this rule, and you should know who may be able to see, use and share your health information for research and why they may need to do so. Information about you and your health cannot be used in this research study without your written permission. If you sign this form, it will provide that permission (or "authorization") to Mayo Clinic.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that the researchers cannot release or use information, documents, or samples that may identify you in any action or suit unless you say it is okay. They also cannot provide them as evidence unless you have agreed. This protection includes federal, state, or local civil, criminal, administrative, legislative, or other proceedings. An example would be a court subpoena.

There are some important things that you need to know. The Certificate DOES NOT stop reporting that federal, state or local laws require. Some examples are laws that require reporting of child or elder abuse, some communicable diseases, and threats to harm yourself or others. The Certificate CANNOT BE USED to stop a sponsoring United States federal or state government agency from checking records or evaluating programs. The Certificate DOES NOT stop disclosures required by the federal Food and Drug Administration (FDA). The Certificate also DOES NOT prevent your information from being used for other research if allowed by federal regulations.

Researchers may release information about you when you say it is okay. For example, you may give them permission to release information to insurers, medical providers or any other persons not connected with the research. The Certificate of Confidentiality does not stop you from willingly releasing information about your involvement in this research. It also does not prevent you from having access to your own information.

Your health information may be collected from:

- Past, present and future medical records.
- Research procedures, including research office visits, tests, interviews and questionnaires.

Your health information will be used and/or given to others to:

- Do the research.
- Report the results.
- See if the research was conducted following the approved study plan, and applicable rules and regulations.

Your health information may be used and shared with:

- Mayo Clinic research staff involved in this study.
- Other Mayo Clinic staff involved in your clinical care.
- Researchers involved in this study at other institutions.
- The sponsor(s) of this study and the people or groups hired by the sponsor(s) to help perform this research.
- The Mayo Clinic Institutional Review Board that oversees the research.
- Federal and State agencies (such as the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health and other United States agencies) or government agencies in other countries that oversee or review research.
- A group that oversees the data (study information) and safety of this research.

How your information may be shared with others:

While taking part in this study, you will be assigned a code that is unique to you, but does not include information that directly identifies you. This code will be used if your study information is sent outside of Mayo Clinic. The groups or individuals who receive your coded information will use it only for the purposes described in this consent form.

If the results of this study are made public (for example, through scientific meetings, reports or media), information that identifies you will not be used.

In addition, individuals involved in study oversight and <u>not</u> employed by Mayo Clinic may be allowed to review your health information included in past, present, and future medical and/or research records. This review may be done on-site at Mayo Clinic or remotely (from an off-site location). These records contain information that directly identifies you.

However, the individuals will not be allowed to record, print, or copy (using paper, digital, photographic or other methods), or remove your identifying information from Mayo Clinic.

Is your health information protected after it has been shared with others?

Mayo Clinic asks anyone who receives your health information from us to protect your privacy; however, once your information is shared outside Mayo Clinic, we cannot promise that it will remain private and it may no longer be protected by the Privacy Rule.

Your Rights and Permissions

Participation in this study is completely voluntary. You have the right not to participate at all. Even if you decide to be part of the study now, you may change your mind and stop at any time. You do not have to sign this form, but if you do not, you cannot take part in this research study.

Deciding not to participate or choosing to leave the study will not result in any penalty. Saying 'no' will not harm your relationship with your own doctors or with Mayo Clinic.

If you cancel your permission for Mayo Clinic to use or share your health information, your participation in this study will end and no more information about you will be collected; however, information already collected about you in the study may continue to be used.

You can cancel your permission for Mayo Clinic to use or share your health information at any time by sending a letter to the address below:

Mayo Clinic
Office for Human Research Protection
ATTN: Notice of Revocation of Authorization
Plummer Building PL 3-02
200 1st Street SW
Rochester, MN 55905

Alternatively, you may cancel your permission by emailing the Mayo Clinic Research Participant Advocate at: researchparticipantadvocate@mayo.edu.

Please be sure to include in your letter or email:

- The name of the Principal Investigator,
- The study IRB number and /or study name, and
- Your contact information.

Your permission for Mayo Clinic to use and share your health information lasts forever, unless you cancel it.

MAYO CLINIC

Name and Clinic Number
Protocol #: 20-008867 **Subject ID:** **Version #:** **Version Date:**

Approval Date: **April 4, 2024**
Not to be used after: **April 3, 2025**

Enrollment and Permission Signatures

Your signature documents your permission to take part in this research.

Printed Name Date (mm/dd/yyyy) Time (hh:mm am/pm)

Signature

Signature of Legally Authorized Representative for Adult Participant

- I give permission for the participant to take part in this research study and agree to allow his/her health information to be used and shared as described above.

Signature Printed Name Relationship to Participant Date \ Time

Person Obtaining Consent

- I have explained the research study to the participant.
- I have answered all questions about this research study to the best of my ability.

Printed Name Date (mm/dd/yyyy) Time (hh:mm am/pm)

Signature