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Protocol Title: Quercetin chemoprevention for Squamous cell carcinoma in patients with Fanconi anemia

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CINCINNATI CHILDREN'S HOSPITAL MEDICAL CENTER
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

STUDY TITLE: Quercetin chemoprevention for Squamous cell carcinoma in patients with Fanconi anemia

FUNDING ORGANIZATION: Fanconi Anemia Research Foundation

INVESTIGATOR INFORMATION:

Name of Principal Investigator:	Telephone Number:
Parinda A. Mehta, MD	(513) 636-5917 during business hours. After business hours please call (513) 636-4200 and ask for the BMT physician on call.

Subject Name: _____ Date of Birth: _____

Throughout this document, references to "You" may stand for either the research study subject or for the parents or legal guardians of the research study subject if the subject is under 18 years of age or otherwise unable to legally give informed consent to participate in the research study. The signature(s) at the end will clarify whether the research study subject is signing this consent form on their own behalf or via a legal guardian or legal personal representative.

INTRODUCTION

You have been asked to participate in a research study. Before agreeing to participate in this study, it is important that you read and understand the following explanation. It describes, in words that can be understood by a lay person, the purpose, procedures, benefits, risks and discomforts of the study and the precautions that will be taken. We may learn new information that may help others in the future. It may or may not have a direct benefit to you. If you decide not to be in this study, we will still take good care of you. If you decide to be in this study, you may change your mind at any time during the study and you can stop being in the study. Take all the time you need to make your choice. Ask us any questions you have. It is also okay to ask more questions after you decide to be in the study. You can ask questions at any time.

WHO IS CONDUCTING THE RESEARCH STUDY?

This study is directed by Parinda Mehta, MD, the researcher at Cincinnati Children's Hospital Medical Center (CCHMC). Medical supervision is provided by Dr. Mehta and physicians of the Cancer & Blood Diseases Institute at CCHMC.

CCHMC has received funds from the Fanconi Anemia Research Foundation, Gateway for Cancer Research, and the Food and Drug Administration grant program to conduct this study.

WHY ARE WE DOING THE RESEARCH STUDY?

The purpose of this research study is to examine the effects of oral quercetin on prevention of squamous cell carcinoma (SCC) in patients with Fanconi anemia (FA) who are post-bone marrow transplant, or adult patients with FA who have not had transplant yet but remain at high risk of squamous cell carcinoma (SCC). Patients with FA cannot tolerate regular chemotherapy and radiation doses used to treat these tumors. This makes surgical removal the only available choice for treatment, which is usually not adequate for cure. In this study, patients will be treated with quercetin, a naturally occurring compound, generally used as a nutritional supplement.

It has also been shown to have a benefit in many types of cancers including SCC.
In our recent study, we have shown that Quercetin is safe and well tolerated (without any major side effects) when given to patients with FA who are pre-transplant, for a long time. A small number of patients with FA were also tested for indicators of DNA damage in their mouth (cheeks) before and after Quercetin treatment. We found that treatment with Quercetin reduced this DNA damage which is thought to lead to the growth of SCC tumors. In addition, a recent study in mice also showed that mice who received Quercetin developed no SCC tumors or very small tumors compared to those who did not receive Quercetin. In our laboratories we also show that Quercetin can kill SCC tumor cells from FA patients.

Based on the above observations, we plan to use Quercetin to prevent growth and/or early progression of SCC in post-transplant patients with FA. We hope this will result in a new method for prevention and/or treatment of SCC in patients with FA.

Quercetin is investigational and has not been definitely confirmed to reduce the risk of developing SCC or other malignancies in patients with FA who have received a bone marrow transplant.

HOW MANY PEOPLE WILL TAKE PART IN THE RESEARCH STUDY?

We expect to enroll approximately 55 subjects in this research study:

- Approximately 45 subjects who have received a bone marrow transplant
- Approximately 10 subjects who have not yet had a transplant

HOW LONG WILL YOU BE IN THE RESEARCH STUDY?

You may be in the research study for up to 2 ½ years. You will be treated with oral quercetin for 2 years or until completion of the 2 year study visit procedures. Approximately 6 months after your 2 year study visit, the doctor may ask you to come to the medical center for an optional study visit for follow-up evaluations at the same time you are due to receive standard follow up care.

The doctor may decide to end your participation in this research study at any time, without your permission, for any of the following reasons: the study doctor determines that it is in your medical best interest, the study is ended early for any reason or new information becomes available.

WHAT WILL HAPPEN IN THE RESEARCH STUDY?

If you agree to participate in this study, the following tests and procedures will be performed, as part of standard clinical care:

- Medical history
- Physical exam, including height and weight
- Blood tests to check liver and kidney function

Additionally, the following research procedures will be performed at the baseline/screening visit:

- Pregnancy test, if applicable: If you are a parent/guardian of a subject who is a minor, you will be notified of the pregnancy results.
- Blood, saliva, and buccal cells (cells from the inside of your cheek) will be collected. You may be tested for COVID-19 along with the collection of the buccal cells. This is to ensure the safety of you and those collecting and processing the buccal cells.
- Exhaled breath test: You will be asked to slowly blow air into a mouthpiece that collects and freezes the sample of the exhaled air from your lungs. You may be asked to wear a nose clip while providing your breath sample, which could take up to 30 minutes to collect.
- Skin elasticity test: You will have a machine attached to part of your skin (most likely the upper arm or forearm) that generates suction. The machine produces suction and warmth, and there may be mild discomfort at the site of the machine attachment to the skin.
- Extra blood sample will be collected for additional future testing
- Adherence Support Session: This session will focus on providing adherence education and introduction to and training on the MyMedSchedule Plus application (see details below) for the patient and if applicable, a parent/caregiver.

Once the doctor has reviewed all required test results and determined that you are eligible to begin taking the study drug, you can expect the following.

Quercetin Administration:

You will be treated with quercetin at a dose based on weight. The total dose will not go beyond 4000 mg/day. Oral quercetin will be taken twice a day for 2 years. Quercetin should be taken at the same times every day. If you miss a dose, you should try to stay on the same dosing schedule. If it is more than 4 hours from the time of your next scheduled dose, take the missed dose. If it is less than 4 hours until the time of your next scheduled dose, just take the next scheduled dose at the regularly scheduled time. Do not take an extra dose.

You will be asked to record each dose in MyMedSchedule Plus**,** the patient interface for MedActionPlan, a HIPAA compliant mobile application that allows patients to track when they have taken their medications. You will be asked to indicate each time you have taken your medication on the MyMedSchedule Plus app throughout the duration of the study. When you have not reported taking your medication in the app, you will receive a notification on your phone reminding you to take your medication. If you have a parent or caregiver, you may also choose for the parent/caregiver to also receive these notifications. Alternate options (i.e. paper diary) may be used for individuals who are unable to use the MyMedSchedule Plus app.

Quercetin compliance will be assessed by the study staff during follow up communication and at each visit. Additionally, the study team will have access to patient reports of medication taken through the HIPAA compliant MedActionPlan Provider Portal, which will be used to review compliance and provide tools for identified barriers to dosing adherence.

All subjects will be closely monitored clinically and any difficulty in tolerating quercetin will be addressed promptly.

Procedures:
You will come to the medical center at 6 months, 1 year and 2 years following the start of quercetin treatment for follow-up evaluations. You will undergo laboratory and clinical evaluation according to standard clinical care (including physical examinations, height/weight, and Ear, Nose and Throat (ENT) and/or Gynecological (GYN) checks, as applicable). ENT and GYN checks may be done locally (near your home) on a case-by-case basis. If you are able to (e.g. live in tristate area) you may be asked to come into the medical center at 1 month for a study visit. If you are not able to come to the medical center, we may ask you to send in samples at 1 month. Additionally, you may be asked to come to the medical center for an optional study visit at 30 months following the start of quercetin treatment.

The following procedures are considered research and will be conducted at each visit.

- Blood, saliva, and buccal cells (cells from the inside of your cheek) will be collected. You may be tested for COVID-19 along with the collection of the buccal cells. This is to ensure the safety of you and those collecting and processing the buccal cells.
- Exhaled breath test: You will be asked to slowly blow air into a mouthpiece that collects and freezes the sample of the exhaled air from your lungs. You may be asked to wear a nose clip while providing your breath sample, which could take up to 30 minutes to collect.
- Skin elasticity test: You will have a machine attached to part of your skin (most likely the upper arm or forearm) that generates suction. The machine produces suction and warmth, and there may be mild discomfort at the site of the machine attachment to the skin.
- Extra blood sample will be collected for additional future testing
- Adherence Support Sessions: These sessions will focus on providing adherence education and adherence feedback to you, as needed, and if applicable, a parent/caregiver. Specifically, you and your parent/caregivers will meet with the study psychologist or her designee during your study visits (in person or virtually) to provide feedback on any barriers regarding your adherence since the last visit using the MedActionPlan data. The psychologist will provide you with tools for overcoming any barriers you are encountering. If you are unable to meet with the study psychologist or her designee during the study visit due to scheduling or any other reason, the adherence support session may be completed virtually up to 30 days after the visit.

These tests may add up to 30-90 minutes to your standard clinical care visit.

In addition to the above procedures, you may be asked to fill out some questionnaires to see how quercetin has affected you. These will be collected prior to your first dose of quercetin, and after 6 months, 1 year, and 2 years of treatment with quercetin.

For the first 6 months, study staff will contact you on a monthly basis to see how you are doing and to review dosing adherence. After 6 months, study staff will contact you every other month until 1 year. From 1 year through the end of the study, study staff will contact you every 3 months. If there is a compliance or any other issue, study staff may contact you more often as needed.

After completing 2 years of treatment with quercetin, participants will have an option to continue quercetin as part of their clinical care. For participants who elect to continue quercetin as part of their clinical care, data from standard clinical care testing will be collected for the study, as available.

WHAT ARE THE GOOD THINGS THAT CAN HAPPEN FROM THIS RESEARCH?

We hope that quercetin may prevent or delay the development of squamous cell carcinoma. It is possible that you may not personally receive medical benefit from participating in this study; however, by taking part in this study you may contribute new information that may benefit patients in the future.

WHAT ARE THE BAD THINGS THAT CAN HAPPEN FROM THIS RESEARCH?

Possible risks and discomforts associated with Quercetin:
Mild to moderate weight gain has been seen in a few subjects currently receiving quercetin on another study. This is usually considered a positive effect for patients with Fanconi Anemia, who are generally small and have difficulty gaining weight.

Drug/food interactions reported with quercetin include the following:

- Digoxin (helps to treat heart failure): increased digoxin levels and side effects of digoxin (sudden death, nausea, vomiting, irregular heartbeat);
- Fluoroquinolones (antibiotics): reduced fluoroquinolone effectiveness has been reported with quercetin.

Patients receiving digoxin therapy and are unable to discontinue this treatment due to medical reasons will not be eligible for study. If you require fluoroquinolones, another similar medication should be used instead.

Potential risks, discomforts, inconveniences associated with drug administration and required evaluations include:

- Blood draws: Blood draws may involve minor pain, bleeding, bruising, and a risk of infection.
- Oral sample collection: Risks associated with oral sample collection include mild discomfort of the cheek area or general discomfort of spitting into a container while the sample is being collected.
- COVID-19 testing: You may be tested for COVID-19 along with the oral sample collection. You may feel some discomfort in the nasal area.
- Exhaled Breath tests: You may be asked to wear a nose clip while providing your breath sample, which could take up to 30 minutes to collect. This may be associated with mild discomfort.

- Skin elasticity tests: There is the possibility of mild pain at the site of suction and blister formation about the size of pencil eraser (3-5mm). The blister should resolve in 5-7 days though skin color changes may not fully resolve until 4-6 weeks, without any permanent effects. There are no restrictions on activities while the blister heals. You will be provided a band-aid or similar covering should you wish to keep the blister covered during the healing process.
- Questionnaires: You may be asked to complete some questionnaires at most of your visits. One of the questionnaires includes questions that may make you feel uncomfortable or upset. You do not need to answer any questions that you do not wish to answer, and you can stop the testing at any time. If you become very upset during the testing at any time, we will end the testing. We will also offer to have you speak to someone about what you are feeling.

The study doctor will monitor your condition closely during the study. If you have any major side effects, treatment may be halted or stopped if your doctor decides that is best. If you develop a suspicious lesion in the mouth or genitourinary region during Quercetin treatment, it will be followed (including biopsied) according to standard clinical care. If you develop SCC, but do not receive any additional therapy other than surgery (e.g. chemotherapy, radiation therapy, or immune therapy), or choose not to receive other therapy, you may be able to continue Quercetin, following appropriate review of the individual situation and with final permission from the doctor.

There is a chance you may have side effects that have not been seen before with the use of quercetin. There also may be risks that are unknown. Your study doctor will tell you if we learn anything that might affect your decision to continue with this study.

WHAT ARE THE REPRODUCTION RISKS?

If you are female and of childbearing potential, you will be tested for pregnancy prior to your first dose of quercetin. Because the drug in this research study may have an effect on an unborn baby, you should not become pregnant or father a baby while in this research study. You should not nurse a baby while in this research study. You should notify your study doctor immediately if you become pregnant or you think you have caused a pregnancy. You should discuss birth control options with the study doctor.

WHAT OTHER CHOICES ARE THERE?

Instead of being in this study, you can choose not to be in it.

Please discuss with the doctor what alternative treatment options might be available for you.

HOW WILL INFORMATION ABOUT YOU BE KEPT PRIVATE?

Making sure that information about you remains private is important to us. To protect your privacy in this research study we will store study data on password protected computers and documents will be stored under lock and key with restricted access to only qualified personnel involved with this research study. You will not be identified in any publication resulting from any research using this data or these samples.

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

The Food and Drug Administration (FDA) may choose to inspect your records since you are a subject in this investigation of a drug not approved for your disease.

WHAT IF WE LEARN NEW INFORMATION DURING THE RESEARCH?

The study doctor will tell you if they find out about new information from this or other studies that may affect your health, safety or willingness to stay in this study.

WILL IT COST YOU ANYTHING EXTRA TO BE IN THE RESEARCH STUDY?

All research costs and expenses related to this study outside of what is indicated for clinical care will be paid for from research funds. This includes the following research procedures:

- Pregnancy test, if applicable
- Sample collection and tests on blood, saliva, and buccal cells
- COVID-19 testing
- Exhaled breath test
- Skin elasticity test
- Extra blood samples for additional future testing

Quercetin will be provided at no cost for 2 years. Travel assistance will be considered only if needed, on a case by case basis. Your study doctor will discuss this with you more thoroughly. Care that is defined as part of the routine clinical care of patients with Fanconi Anemia, including but may not be limited to: physical examinations, height/weight, and Ear, Nose and Throat and/or Gynecological assessments, will be your or your insurance carrier's responsibility. You or your insurance company will be charged for hospitalization including tests and treatments of any side effects of quercetin. In the event that your insurance does not cover these costs, you may incur additional costs because of treatment side effects.

WILL YOU BE PAID TO BE IN THIS RESEARCH STUDY?

Study staff will review dosing adherence and documentation throughout the study duration and at study visits. You will receive $15 per month for compliant use of the MyMedSchedule Plus app between each study follow up visit. You will be sent payment in between visits via ClinCard and the ClinCard will be reloaded at each compliance review if you meet compliance requirements. In order to be considered compliant within the MyMedSchedule Plus app, doses taken must be logged twice daily in the app on the same day the doses are taken 75% of the time each month. Additionally, at each follow up study visit if you meet compliance requirements, you will receive $50 at the 6-month visit, $60 at the 1-year visit, and $75 at the 2-year visit. Dosing adherence will be determined by review of dosing documentation in the MyMedSchedule Plus app.

You will receive payment for this study in the form of a reloadable debit card (ClinCard). We will give you a handout that will explain how to use the card. Because you are being paid for your participation, Cincinnati Children's is required by the Internal Revenue Service (IRS) to collect and use your social security number (SSN) or taxpayer identification number (TIN) to

track the amount of money that we pay. You will need to complete a Federal W-9 form for this income tax reporting. This form requires your Social Security number. This form will be given to the Cincinnati Children's business office. It will not be kept as part of your study chart. If you move, you will need to complete another W-9 with an updated address.

If you do not have a social security number or tax identification number, you will be offered gift cards in the amounts specified above.

WHAT HAPPENS IF YOU ARE INJURED FROM BEING IN THIS STUDY?

If you believe that you have been injured as a result of this research you should contact Dr. Parinda Mehta as soon as possible to discuss the concerns. Treatment for injuries is available at CCHMC. If you go to the Emergency Room or to another hospital or doctor it is important that you tell them that you are in a research study. If possible, you should give them a copy of this consent form.

CCHMC follows a policy of making all decisions about compensation for the medical treatment of physical injuries that happened during or were caused by research on an individual basis.

WHAT ARE YOUR RIGHTS AS A PARTICIPANT?

Your participation in this study is completely **voluntary**. You may choose either to take part or not to take part in this research study. Your decision whether or not to participate will not result in any penalty or loss of benefits to you and the standard medical care for your condition will remain available to you.

If you decide to take part in the research study, you are **free to withdraw** your consent and discontinue your participation in this research study at any time. Leaving the study will not result in any penalty or loss of benefits to you. If your participation is stopped, you should go through the study termination procedures for your own safety.

If you have questions about the study, you will have a chance to talk to one of the study staff or your regular doctor. Do not sign this form unless you have had the chance to ask questions and have received satisfactory answers.

Nothing in this consent form waives any legal rights you may have nor does it release the investigator, the sponsor, the institution, or its agents from liability for negligence.

WHO DO YOU CALL IF YOU HAVE QUESTIONS OR PROBLEMS?

For questions, concerns, or complaints about this research study you can contact the study person listed on page 1 of this document. If you would like to talk to someone that is not part of the research staff or if you have general questions about your research study rights or questions, concerns, or complaints about the research, you can call the CCHMC Institutional Review Board at 513-636-8039.

WHAT ELSE SHOULD YOU KNOW ABOUT THE RESEARCH?

If you come off study early for any reason, including personal reasons, you will be asked to discontinue treatment as soon as possible. You may be asked to complete an end of study visit. Every effort will be made to complete this visit at the same time as an already scheduled clinical visit. If you do not have an already scheduled clinical visit, you may be asked to come to CCHMC to provide samples if you are local. If you are not local or cannot come to CCHMC for an end of study visit, you may be asked to provide samples via mail. Study staff may also call you to review your general health status, the reason why you decided to stop the study (if applicable), and to discuss a plan to return any remaining quercetin and study diaries.

The study doctor may recommend to discontinue your participation in the study at any time. The study doctor will explain the reason for this recommendation and suggest alternative options.

AUTHORIZATION FOR USE/DISCLOSURE OF HEALTH INFORMATION FOR RESEARCH

To be in this research study you must also give your permission (or authorization) to use and disclose (or share) your “protected health information” (called PHI for short).

What protected health information will be used and shared during this study?
CCHMC will need to use and share your PHI as part of this study. This PHI will come from:

- Your CCHMC medical records
- Your research records

The types of information that will be used and shared from these records include:

- Laboratory test results, diagnosis, and medications
- Reports and notes from clinical and research observations
- Imaging (like CT scans, MRI scans, x-rays, etc.) studies and reports
- If applicable, information concerning HIV testing or the treatment of AIDS or AIDS-related conditions, drug or alcohol abuse, drug-related conditions, alcoholism, and/or psychiatric/psychological conditions (but not psychotherapy notes).

Who will share, receive and/or use your protected health information in this study?

- Staff at all the research study sites (including CCHMC)
- Personnel who provide services to you as part of this study
- Other individuals and organizations that need to use your PHI in connection with the research, including people at the sponsor and organizations that the sponsor may use to oversee or conduct the study.
- The members of the CCHMC Institutional Review Board and staff of the Office of Research Compliance and Regulatory Affairs.

How will you know that your PHI is not misused?
People that receive your PHI as part of the research are generally limited in how they can use your PHI. In addition, most people who receive your PHI are also required by federal privacy laws to protect your PHI. However, some people that may receive your PHI may not be required to protect it and may share the information with others without your permission, if permitted by the laws that apply to them.

Can you change your mind?
You may choose to withdraw your permission at any time. A withdrawal of your permission to use and share your PHI would also include a withdrawal from participation in the research study. If you wish to withdraw your permission to use and share PHI you need to notify the study doctor, listed on the first page of this document, in writing. Your request will be effective immediately and no new PHI about you will be used or shared. The only exceptions are (1) any use or sharing of PHI that has already occurred or was in process prior to you withdrawing your permission and (2) any use or sharing that is needed to maintain the integrity of the research.

Will this permission expire?
Your permission will expire at the end of the study. If the study involves the creation or maintenance of a research database repository, this authorization will not expire.

Will your other medical care be impacted?
By signing this document you are agree to participate in this research study and give permission to CCHMC to use and share your PHI for the purpose of this research study. If you refuse to sign this document you will not be able to participate in the study. However, your rights concerning treatment not related to this study, payment for services, enrollment in a health plan or eligibility of benefits will not be affected.

SIGNATURES

The research team has discussed this study with you and answered all of your questions. Like any research, the researchers cannot predict exactly what will happen. Once you have had enough time to consider whether you should participate in this research you will document your consent by signature below.

You will receive a copy of this signed document for your records.

_____	_____
Signature of Research Participant Indicating Consent	Date
_____	_____
Signature of Parent or Legally Authorized Representative*	Date

_____

* If signed by a legally authorized representative, a description of such representative's authority must be provided.

_____	_____
Signature of Individual Obtaining Consent	Date

The signature line below is to be used only when an interpreter or a witness is required for the consent process.

_____	_____
Signature of Person Present During Consent	Date