INSTITUT DE CARDIOLOGIE DE MONTRÉAL

AFFILIÉE À Université de Montréal

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APPROUVÉ / APPROVED
Comité d'éthique ICM
MHI – Research Ethics Board
Date : 13 avril 2023

INFORMATION AND CONSENT FORM

Research study: MP-33-2021-2761

Title of the study: Q-CABG – Randomized Placebo-Controlled Phase II Clinical Trial to Study the Anti-Inflammatory and Senolytic Activities of Quercetin During Coronary Artery By-pass Graft Cardiac Surgery

Principal investigator: Michel Carrier, MD

Co-Investigator: Eric Thorin, PhD

Collaborators: Pierre-Emmanuel Noly, MD, Louis P. Perrault, MD.

Granting agency: Canadian Institutes of Health Research

PREAMBLE

We are inviting you to take part in this research study because you have a blocked coronary artery requiring a surgical intervention in the following days to by-pass this obstruction and restore the blood flow in the muscle of your heart. You are entirely free to accept or refuse to participate.

Before you agree to take part in this project and sign this information and consent form, please take the time to carefully read, understand and consider the following information.

This form may contain words that you do not understand. We invite you to ask the investigator in charge of the project or the other staff members involved in the research study any questions you consider useful and ask them to explain any word or information that is not clear to you.

Taking part in several research studies at the same time may be dangerous. If you are already taking part in a clinical study, please notify the study doctor.

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NATURE AND OBJECTIVES OF THE RESEARCH STUDY

The surgery is associated with an important inflammation. This is a consequence of the intervention and is normal, and contributes to the healing after the surgery; if too important, however, it can delay the recovery of the patients. This inflammation is characterized, among other thing, by an increase in the white blood cell count in your blood.

Quercetin, a natural health product approved by Health Canada and in free-access in pharmacies, is an organic product contained in fruits, vegetables and red wine. It is therefore, a natural product that you ingest regularly while eating vegetables. The dietary intake is, however, highly variable in the population, and is estimated to be between 10 and 100 mg per day. Quercetin is a source of antioxidant, and possess anti-inflammatory and antioxidant effects well demonstrated in laboratory studies and in animals. However, few studies using quercetin as a supplement for medical use have been performed in humans. A few studies have been performed in people with cardiovascular diseases, including with increase in blood pressure, in cholesterol and with inflammation associated with a stable coronary artery disease, but none in patients with severe coronary artery diseases requiring a bypass surgery.

The objective of the study is to investigate the anti-inflammatory effects of quercetin 4 days after the surgery in patients with coronary artery disease. The secondary objective of the study is to investigate the consequences of quercetin on the cells of the the mammary artery used during the surgery to by-pass the obstruction of the coronary artery. During the surgery, the surgeon will cut and discard a fragment of this mammary artery to fit its length below the diseased area of the coronary artery, and the scientists will collect this discarded segment for the analyses.

As of today, there is no treatment that reduces the excess of inflammation and prevents its side effects after cardiac surgeries.

NUMBER OF PARTICIPANTS AND LENGTH OF PARTICIPATION

The study will include 120 patients, men and women of 18 years of age or more, recruited in 2 centers across Québec.

All patients will be operated at the Montreal Heart Institute. These patients will be hospitalized at the Montreal Heart Institute, or will have been referred from the *Centre hospitalier affilié universitaire régional (CHAUR) de Trois-Rivières (CIUSSS de la Mauricie-et-du-Centre-du-Québec)*. The latter patients will have started the treatment with quercetin before the transfer to the Montreal Heart Institute the day before the surgery.

Quercetin will be administered only during your hospital stay; you will not have to take it after your hospital discharge.

RESEARCH STUDY FUNDING

The co-investigator in charge of the project has received funding from a granting agency, Canadian Institutes of Health Research, for conducting this research study.

RESEARCH STUDY PROCEDURES

The study we are proposing to you is a randomized clinical study, that is, you will have a one in two chance of receiving either quercetin or a placebo, that is, an inactive and harmless product.

In this study, both quercetin and placebo are referred to as the "study drug". You will be given the quercetin or the placebo on a random assignment, such as a coin toss. Neither you nor the study researchers will know which of the study drugs you will be assigned to. However, your doctors will be able to obtain this information if they deem it necessary for your health.

If you agree to participate in the study, the research team will take some of your time to complete a demographic questionnaire with you. This questionnaire will allow you to better understand your health history. Two days before your surgery, a blood test will be taken as a reference on an empty stomach; it will help measuring the effect of the study medication on your inflammatory response afterward. This blood test will therefore be repeated 24 hours, four days after your surgery and when you are discharged from the hospital (or up to a maximum of seven days after the operation). About five ml per blood test will be taken, the equivalent of a teaspoon. The research team will make sure that the blood tests match the usual blood tests.

From the day before or the day before your surgery until your discharge from the hospital, you will receive from the nursing staff and twice a day, the medicine (a dose of 500 mg morning and evening) studied or placebo. You will have no other responsibility than taking the two capsules each day while you are in the hospital.

During your surgery, a segment of the mammary artery that has been rejected will be collected for analysis by researchers. Your surgery will proceed without any other changes. All participants will undergo their surgery according to the classic and recognized approaches of best medical practice.

Your participation in the research project takes place while you are hospitalized and will not require an additional visit to the hospital after your discharge. You will only be given study medication during your stay in the hospital. Your stay in the hospital will not be extended in any way.

On four occasions during your hospitalization, we will take a blood test to measure the effect of the medication on your inflammatory response. These blood samples will not be used for further testing and will be destroyed once the testing is complete.

After your follow-up visit (8-12 weeks post-surgery), a member of the research team will consult your medical file to identify any remarkable medical information that may have occurred during your convalescence.

Your doctors and surgeon will give you all the usual care required by your condition. Your participation in the study does not affect the clinical care you will receive.

The following table summarizes your participation in the research study.

Procedures	**Visite of selection**	Treatment initiation (2 days before surgery)	**Surgery day**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Following days**	**Hospital discharge (or maximum day 7)**
Consentement	X									
Demographic survey	X									
Randomization	X									
Administration of study drug (twice a day)		X	X	X	X	X	X	X	X	X
Blood sampling		X		X			X			X
Mammary artery sampling			X							

PARTICIPANT'S RESPONSIBILITIES

Your only responsibility in this project is to take the study medication twice a day, in the morning and in the evening.

RISKS ASSOCIATED WITH THE RESEARCH STUDY

By participating in this research study, you may be exposed to particular unknown, unexpected or unforeseeable risks. The purpose of this section is to describe the foreseeable risks associated with your participation in this research study.

The risks associated with the routine clinical treatments that you are receiving have already been explained to you by a doctor and are not described in this section because they are not part of the research.

Risks associated with the mammary artery segment: Regarding the removal of a segment of the mammary artery, there is no risk associated with this procedure since this piece of vessel is usually rejected. In addition, there is no risk associated with the messenger RNA analyzes that will be done from the mammary artery segment.

Allergy Risks: The risks of allergies to this natural product are minimal, but they may be present. The research team will make sure that you do not have a known drug allergy. You cannot participate in the study if you have a history of allergy to niacin, ascorbic acid (vitamin C), if you have impaired kidney or liver function or if you have a history of cancer of the breast or other estrogen-dependent tumor. Since you will only be taking the study medication while you are in hospital, the healthcare team will watch for any allergic reactions, including redness, itching, swelling, nausea and / or vomiting, and difficulty in breathing. In the event of an allergic reaction, the research team will discontinue your participation in the study. Obviously, you will have the care you need for your state of health at all times.

Risks Associated with Blood Tests: Blood tests usually have no side effects. You may feel a small sting or burning when inserting the needle into the vein in your forearm. Others experience mild vagal discomfort when withdrawing the needle. In very rare situations, especially with difficult samples (leaky veins, moving needle) a little swelling or a bruise may form at the site of the sample which will disappear within a few days.

Risks associated with side effects of the medication under study: Studies in sports medicine, particularly in athletes and soldiers, on quercetin show that an additional intake to the amount already present in the diet does not cause any notable side effect and known for short-term use ranging from a few days to a few weeks. Furthermore, few studies have been carried out in people with mild cardiovascular diseases and no risks associated with quercetin in this category of patients have been reported. During your participation in this study, you will be closely monitored during your stay in the hospital for any side effect you may have, and all necessary care will be given to you in such a case.

COVID-19 pandemic

With the situation of the COVID-19 pandemic, risks related to the spread of the virus may be incurred during travel and by going to the research center. The staff has taken necessary measures to protect you and minimize the risks. Infection prevention and control rules are strictly applied, whether in connection with the wearing of personal protective equipment, hand hygiene and the disinfection of surfaces and equipment.

RISKS RELATED TO PROCREATION

Participation in this research study may involve unknown risks for pregnant women, unborn children or breastfed infants. Consequently, pregnant or nursing women cannot participate in this project.

Women of childbearing potential must undergo a pregnancy test before they start participating in the project. Additional pregnancy tests will be performed throughout the research to ensure that you have not become pregnant during your participation in the project.

The investigator in charge or the research study staff will check your birth control method to ensure that it is medically acceptable.

If you think that you have become pregnant during your participation in this project, you will need to notify the investigator in charge of the research study immediately in order to discuss the various options.

BENEFITS

You may personally benefit from your participation in this research study, but this cannot be guaranteed. However, the results obtained will contribute to furthering scientific knowledge in this field.

OTHER POSSIBLE TREATMENTS

There is no drug known to significantly decrease the inflammatory response after heart surgery.

PROCEDURE IN THE EVENT OF DEATH

In the event of your death while participating in this research study, it may be useful for the research study investigator and the sponsor to obtain information about your health condition at the time of your death and the causes of your death. For this purpose, you may authorize the project investigator to obtain a copy of your medical record from another health care or extended care facility. This may include a copy of your record from the emergency department or from any department of another hospital, nursing home or medical clinic. The information collected will only be used for the purposes of this research and will remain confidential. It may be shared with the sponsor or granting agency of this study.

VOLUNTARY PARTICIPATION AND THE RIGHT TO WITHDRAW

Your participation in this research study is voluntary. Therefore, you may refuse to participate. You may also withdraw at any time, without giving any reasons, by informing the doctor in charge of this research study or a member of the research team.

Your decision not to participate in the study, or to withdraw from it, will have no impact on the quality of care and services to which you are otherwise entitled, or on your relationship with the teams providing them.

The doctor in charge of this research study, the Research Ethics Board, the funding agency, or the sponsor may put an end to your participation without your consent. This may happen if new findings or information indicate that participation in this research study

is no longer in your best interests, if you do not follow study instructions, or if there are administrative reasons to terminate the study.

If you opt out of the project or are withdrawn from the project, the information and material already collected as part of this project will still be retained, analyzed or used to ensure the integrity of the project.

If you withdraw or are withdrawn from the study, no further data or samples will be collected. However, the information and biological material, blood and tissue samples, collected for the study will be stored, analyzed and used to ensure the integrity of the study, as described in this document.

Any new findings acquired during the course of the study that could influence your decision to continue your participation will be shared with you quickly.

CONFIDENTIALITY

During your participation in this study, the doctor in charge of the study and the research team will collect, in a study file, the information about you needed to meet the scientific objectives of the study.

The study file may include information from your medical charts including your identity, such as your name, gender, date of birth, ethnicity, past and present health status, lifestyle, and the results of all tests, exams, and procedures that will be performed.

All study data collected during this research study (including personal information and samples) will remain confidential to the extent provided by law. You will be identified by a code number only. The key to the code linking your name to your study file will be kept by the doctor in charge of this research study.

To ensure your safety, the signed consent form indicating your participation in this study is included in your medical chart. The results of certain tests conducted as part of the research may be included as well, depending on the situation. As a result, any person or company to whom you give access to your medical chart will have access to this information.

You will only be identified by a code number. The key to the code linking your name to your research file will be kept by the doctor responsible for this research project.

Study data will be stored for at least 15 years following the end of the study by the doctor in charge of this research study.

Blood samples and mammary artery segments obtained at participating centers and at the Montreal Heart Institute will be sent to Dr. Thorin's laboratory (Montreal Heart Institute) for analysis.

Encoded blood samples will be kept until the time of analysis and subsequently destroyed.

The coded mammary artery segment will be used to study vascular reactivity (relaxation) and another segment will be used to measure mRNA expression in each of the cells individually. After the measurements, the mammary artery segments will be destroyed immediately.

The study data may be published or shared at scientific meetings; however, it will not be possible to identify you.

For monitoring, control, safety, security, and approval of the study drug by regulatory agencies, your study file as well as your medical charts may be examined by a person mandated by Canadian or international regulatory authorities, such as Health Canada, the institution, or the Research Ethics Board. All these individuals and organizations will have access to your personal data, but they adhere to a confidentiality policy.

You have the right to consult your study file in order to verify the information gathered, and to have it corrected if necessary.

However, to protect the scientific integrity of this study, you may have to withdraw from the study if you access certain information before the study ends.

COMMUNICATION OF GENERAL RESULTS

You will be able to find out about the general results of this study if you ask the principal investigator at the end of the study.

SHOULD YOU SUFFER ANY HARM

Should you suffer harm of any kind following administration of the study drug or any other procedure related to this research study, you will receive all the care and services required by your state of health.

By agreeing to participate in this research study, you are not waiving any of your rights nor discharging the doctor in charge of the study, the sponsor, or the institution of their civil and professional responsibilities.

COMPENSATION

You will not receive financial compensation for participating in this research study.

CONTACT INFORMATION

If you have any questions or if you have a problem you think might be related to your participation in this research study, or if you would like to withdraw, you may communicate with the doctor in charge of this research study or with someone on the research team at the following numbers:

Montreal Heart Institute

Michel Carrier MD, Investigator: ..... Tel.: 514 376-3330 (ext. 3715)

Research team (E. Thorin): ..... Tel.: 514 376-3330 (ext. 3589)

For any questions regarding your rights as a research participant in this study, or if you have comments or wish to file a complaint, you may communicate with:

The local service quality and complaints commissioner
Montreal Heart Institute
5000 Bélanger Street
Montreal (Quebec) H1t 1c8
Telephone: 514 376-3330, ext. 3398

The Research Ethics Board of the Montreal Heart Institute Research Ethics and New Technology Development Board has given ethics approval to this research study and is responsible for monitoring the study at all participating institutions in the health and social services network in Quebec.

INFORMATION ABOUT THE STUDY ON A WEBSITE

A description of this study is available in English only at http://www.ClinicalTrials.gov. This site contains no information which can identify you. At most, the site will include a summary of the results when they are available. You may consult this site at any time. This project's registration number is NCT04907253.

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CONSENT FORM

Research study: MP-33-2021-2761

Title of the study: Q-CABG – Randomized Placebo-Controlled Phase II Clinical Trial to Study the Anti-Inflammatory and Senolytic Activities of Quercetin During Coronary Artery By-pass Graft Cardiac Surgery

Principal investigator: Michel Carrier, MD

Co-Investigator: Eric Thorin, PhD

Collaborators: Pierre-Emmanuel Noly, MD, Louis P. Perrault, MD.

Granting agency: Canadian Institutes of Health Research

SIGNATURE OF PARTICIPANT

I have reviewed the Informed Consent Form. Both the research study and the Informed Consent Form were explained to me. My questions were answered, and I was given sufficient time to make a decision. After consideration, I consent to participate in this research study in accordance with the conditions stated in this form.

I authorize the study team to have access to my medical record.

☐ Yes Initials: _____

☐ No Initials: _____

Communication with the participant regarding future research

I authorize the researcher in charge of this study to communicate with me to see if I am interested in participating in other research studies.

☐ Yes Initials: _____

☐ No Initials: _____

Name of participant	*Signature*	*Date (dd-mm-yyyy)*

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SIGNATURE OF THE PERSON OBTAINING CONSENT

I have explained the research study and the terms of this Informed Consent Form to the research participant, and I answered all questions asked.

Name of the person obtaining consent	***Signature***	***Date (dd-mm-yyyy)***

COMMITMENT OF THE PRINCIPAL INVESTIGATOR

I certify that this Informed Consent Form was explained to the research participant, and that the participant's questions were answered.

I undertake, together with the research team, to respect what was agreed upon in the Informed Consent Form, and to give a signed and dated copy of this form to the research participant.

Name of the principal investigator	***Signature***	***Date (dd-mm-yyyy)***

SIGNATURE OF WITNESS

☐ **YES** ☐ **NO**

A witness's signature is required in the following cases:

- ☐ Reading disability or inability to read – The witness (impartial) signing below attests to the fact that they read the Informed Consent Form, that the study was precisely explained to the participant, and that the participant seems to have understood it.
- ☐ Foreign language (participant does not understand the language in which the Informed Consent Form was written) – The signatory attests to acting as interpreter for the participant throughout the consent process.

Name of witness	***Signature***	***Date (dd-mm-yyyy)***

N.B.: A signed and dated copy of this patient information and consent form will be placed in the participant's file, a copy kept by the principal investigator and a copy given to the participant.

CONSENT OF THIRD PARTY LEGALLY AUTHORIZED TO CONSENT IN LIEU OF A PARTICIPANT WHO IS INCAPACITATED

As the legal representative of the participant (guardian, trustee, mandatary; or in cases of sudden incapacity, spouse, close relative, or person close to the participant), I have reviewed the Informed Consent Form. The study and the Informed Consent Form were explained to me. My questions were answered, and I was given sufficient time to decide.

I was also informed that in the event that the person I represent becomes able to give consent for themselves while this research study is underway, that person will be invited to sign the Informed Consent Form.

After reflection, I consent that the person I represent may participate in this research study in accordance with the conditions stated above, including the use of personal data and samples. I will receive a copy of this consent form, signed and dated.

I authorize the research team to access the medical chart of the person I represent. I also authorize the researcher or their team to inform the person's family doctor or treating physician that that the person I represent is taking part in this research study and to send them all relevant information.

Name of research participant represented:

_____

Name of legal representative:

_____ (guardian, trustee, mandatary, spouse, close relative or person close to the participant) *specify below:*

- ☐ Trustee
- ☐ Guardian
- ☐ Mandatary
- ☐ Spouse
- ☐ Close relative
- ☐ Person close to the participant

_____ _____

Signature of legal representative **Date**

SIGNATURE OF THE PERSON OBTAINING CONSENT

I have explained the terms of this Informed Consent Form to the legal representative, and I answered all questions asked.

Name of the person obtaining consent	***Signature***	***Date (dd-mm-yyyy)***

COMMITMENT OF THE PRINCIPAL INVESTIGATOR

I certify that the terms of this Informed Consent Form were explained to the legal representative, that their questions were answered, and that it was clearly indicated that he can withdraw the participant he represent from the study at any time.

I undertake, together with the research team, to respect what was agreed upon in the Informed Consent Form, and to give a signed and dated copy of this form to the legal representative.

Name of the principal investigator	***Signature***	***Date (dd-mm-yyyy)***

SIGNATURE OF WITNESS

☐ **YES** ☐ **NO**

A witness's signature is required in the following cases:

- ☐ Reading disability or inability to read – The witness (impartial) signing below attests to the fact that they read the Informed Consent Form, that the study was precisely explained to the participant, and that the participant seems to have understood it.
- ☐ Foreign language (participant does not understand the language in which the Informed Consent Form was written) – The signatory attests to acting as interpreter for the participant throughout the consent process.

Name of witness	***Signature***	***Date (dd-mm-yyyy)***

SIGNATURE OF PARTICIPANT HAVING REGAINED DECISION-MAKING CAPACITY

I have examined the Informed Consent Form and I understand that my legally authorized representative has accepted, on my behalf, that I participate in this research study. I attest that the research study and this Informed Consent Form were explained to me, that my questions were answered to my satisfaction, and that I was given enough time to decide.

After reflection, I consent to continue participating in this research study in accordance with the conditions stated above, including the use of my personal data and my samples. I will receive a copy of this Informed Consent Form, signed and dated.

I authorize the research team to access my medical chart for the purposes of this research study. I also authorize the researcher or their team to inform my family doctor or treating physician, in writing, that I am taking part in this research study, and to send them all relevant information.

Please check the appropriate box to indicate your decision:

☐ I wish to remain in this research study.

☐ I wish to withdraw from this research study.

Name of participant	***Signature***	***Date (dd-mm-yyyy)***

Name of witness* / relationship with participant	***Signature***	***Date (jj-mm-aaaa)***

** The signature of a witness is required: 1) in addition to the participant's, if the Informed Consent Form is read to the participant; or 2) instead of the participant's, if the participant is legally capable of consent but is unable to read or write (e.g., the witness signs beside the participant's thumbprint).*

SIGNATURE OF THE PERSON OBTAINING CONSENT

I have explained the research study and the terms of this Informed Consent Form to the research participant, and I answered all questions asked.

Name of the person obtaining consent	***Signature***	***Date (dd-mm-yyyy)***

COMMITMENT OF THE PRINCIPAL INVESTIGATOR

I certify that this Informed Consent Form was explained to the research participant, and that the participant's questions were answered.

I undertake, together with the research team, to respect what was agreed upon in the Informed Consent Form, and to give a signed and dated copy of this form to the research participant.

Name of the principal investigator	***Signature***	***Date (dd-mm-yyyy)***