The Graviola Study

The safety and tolerability of *Annona muricata* leaf extract in people living with cancer

1 Would you like to take part in this clinical study?

We would like to invite you to take part in a clinical study evaluating the effects of a herbal product in people living with cancer who are 18 years of age and older

This document tells you about the study and describes what will happen if you take part. If there is anything you don't understand or want to know more about, please ask us.

You might also want to talk to a relative, a friend or your GP before you make up your mind. You may also take this form away with you. If you decide to go ahead, we will ask you to sign the consent form (*the last page of this document*).

2 Why are we doing this research?

In this study, we aim to determine if a herbal product containing Graviola (*Annona muricata)* is safe and well tolerated by people living with cancer and to determine if it has any effects on your immune function.

The study treatment is a herbal product containing dried leaf extract of Graviola (*Annona muricata)*. This herbal product has been widely used by people living with cancer in the Caribbean and South American region. Case reports have suggested that *Annona muricata* was associated with an improvement in cancer progression. Previous clinical trials conducted in people living with cancer suggest that graviola is safe to use.

This experimental herbal product Graviola (brand name Swanson Inc.), is a commercially available dietary supplement listed with the United States Food and Drug Administration (FDA). It has not been approved for use in the management of people living with cancer. It is manufactured by UST corporation, Inc., a Good Manufacturing Practice (GMP) certified company. Graviola (*Annona muricata*) is not currently listed on the Australian Register of Therapeutic Goods, hence, the safety of its use in people living with cancer must be tested.

3 Do I have to take part?

If you don't wish to take part in the clinical study, you don't have to. If you decide to take part and later change your mind, you are free to withdraw at any stage. If you choose not to take part, or if you choose to take part and then later withdraw, you will still be able to access your usual medical care. Your choice will not affect your relationship with those treating you, or with this institution.

If you choose not to join the study, the study doctor will discuss other options with you.

We must keep any information we collect about you, up until you withdraw. Concord Repatriation General Hospital and the University of Sydney has access to this information so they can check it is correct. If you do not agree with this then we cannot allow you to join the clinical study.

4 What is involved in the study?

For this study, we are seeking male and female participants who have been diagnosed with metastatic or recurrent cancer (stage III or IV) and aged ≥ 18 years of age, who are not actively being treated or are no longer eligible for standard cancer treatments.

If you choose to take part in this study, you will be assigned to one of the two groups, group 1 and 2 will both have 12 participants. The total number of participants is 24. This study will be carried out primarily at the Concord Repatriation General Hospital. Depending on the group you are assigned at, you will be required to either take 1 capsule of Graviola (*Annona muricata* daily) (group 1) or 1 capsule twice daily (group 2). The medication will be scheduled to be taken before breakfast and dinner. You will need to record the number of capsules and ingestion times daily in a participant dosing diary. The treatment duration is 12 weeks. The study treatment is provided along-side the usual care provided by your oncologist.

While taking Graviola (*Annona muricata)*, you will be required to visit the clinic five times, to assess how you are tolerating the treatment. During the visit, the clinical trial doctor will conduct standard neurological examination. Your disease status, carcinoembryonic antigen (CEA), immune, liver and kidney function will also be assessed by measuring your full blood count and immune cells through blood test. Each visit will require 30 to 60 minutes of your time. You will be required to complete a quality-of-life questionnaire (taking around 12 minutes to complete) while in the waiting room prior to each visit and keep a daily diary of any symptoms you may experience. Blood pressure and blood tests (around 40 mL or 4 standard tubes) will be taken at each of the visits to determine the impact of Graviola (*Annona muricata*) on your immune system. Some of these blood tests will be taken as part of your standard care. In week 6 and 12 (visit 3 and 5), you are required to return the study drug container containing any unused capsules, in addition to the participant doing diary during your clinic study. This will help us understand how compliant you have been with taking the medicine.

In an event you miss a dose, you will be advised to wait until the next scheduled dose

In addition to your personal clinical results and furthering the body of knowledge of this area, a lay summary of the overall outcome of the study will be provided to all participants. Participants will also be made aware of any publications arising from this study.

Table of clinic visits and assessments

Clinic Visits	**Screening visit**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
Time point	Before joining the study	On joining the study	3rd Week	6th Week	9th Week	12th Week
Occurrence	Before treatment	Before treatment	During treatment	During treatment	During treatment	End of treatment
Neurological examination	✓	✓	✓	✓	✓	✓

Blood tests/ blood pressure	✓	✓	✓	✓	✓	✓
Questionnaires (Quality of life)		✓	✓	✓	✓	✓
Self- report symptom diary & Participant dosing diary			Daily- Throughout the study			

*Tests included in standard care with results analysed as part of the study

Your eligibility of inclusion of the trial will be assessed by the CT doctor and/or the clinical trial team.

5 Who is conducting and paying for this research?

This is an investigator-initiated research, funded by the Concord Cancer Centre and supported by in-kind contributions from the Sydney School of Pharmacy and the subject of a PhD project (University of Sydney). There is no conflict of interest to declare in this study. The study will be conducted in accordance with the International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) Guidelines.

All treatment, medication and study-related tests will be provided at no cost to you. You should ask the study doctor to explain any payments for which you may be responsible unrelated to the clinical trial. The study will be monitored for compliance by the Coordinating Principal Coordinator (CPC). Any adverse effects will be reported to the clinical trial doctor by the participants and will be reviewed by the clinical trial Safety Review Committee.

6 What if something new comes up during the study?

If we find something new about Graviola (*Annona muricata)* while the study is under way, the study doctor will discuss with you what it means and whether you want to continue in the study. If you decide to continue in the clinical study, we will ask you to sign an updated consent form.

7 What will happen to the confidential information about me?

We will keep any personal information we collect about you confidential and securely stored. The clinical data we collect will be coded. No information that can identify you such as your name and address will leave the clinic. Any information relevant to the study question (e.g. blood test results or questionnaires) and included in the data analysis will be de-identified prior to analysis by the research team. Only group data will be published, no individual data will be published. All data analysed by the research team will be deidentified.

8 What information will be collected, and how will it be stored?

Australian and New South Wales privacy law gives you the right to request access to your information that the researchers have collected and stored. The law also gives you the right to request corrections to any information about you that you disagree with. Please contact the study team (see page 8 of this document) if you would like to access your information.

We will not disclose your information without your permission, except in compliance with the law. Information about you may be obtained from your health records held at this institution and may be obtained from other health services for the purposes of research. Should you wish to cease treatment we would like the option to maintain follow up. If you sign the consent form, you agree to the study team accessing health records if they are relevant to your participation in this study.

We are seeking your approval for members of the research team to access your medical records to allow for assessment of your general health, cancer diagnosis, stage and previous cancer treatment. This

information includes age, gender, weight, height, ethnic background, blood count and biochemical information, clinical information (medical records and treatments).

Information collected including non-digital or hard-copy data such as questionnaires will be stored in Bridge Road Stanmore, Sydney (storage site for Concord hospital) for 15 years then destroyed confidentially. Electronic data will remain in the password protected format in RedCap database and only the research team will have access for the period of 15 years.

Your records relating to this study and any other information received will be kept strictly confidential. However, staff participating in your care, the sponsor and other agencies authorised by law, may inspect the records related to the study. In the event you are admitted to hospital as a result of an adverse event resulting from this study, your treating doctor may require access to your study records.

Your identity will not be revealed, and your confidentiality will be protected in any reviews and reports of this study which may be published. However, results may be suppressed for commercial reasons as the sponsor of the project retains the rights to the data.

Your treating Doctor/s will be notified of your participation in this study and of any clinically relevant information noted by the trial doctor in the conduct of the trial.

The re-identifiable/coded (it is possible to use the code to re-identify you) information held by the sponsor however, will not be destroyed.

Some of your blood sample will be stored and used for further analysis and research at a later date. This sample will be stored for up to 2 years and used for measuring the amount of the active compound annonacin and its breakdown products (metabolites).

9 What are my responsibilities during the study?

If you agree to participate in this study, you agree to be responsible for taking Graviola (*Annona muricata)* according to our instructions. You also agree to comply with the other conditions in this document. If you cannot, or do not wish to accept this responsibility, then we cannot accept you as a participant in the study.

While you are taking Graviola (*Annona muricata)*, you will not require any lifestyle or dietary restrictions. Throughout the study we will monitor your health and safety through routine blood tests and assessments at regular clinic visits which will identify any adverse reactions that may occur.

10 Can I have other medicines or procedures during this clinical study?

You can continue to take your regular medications for any other health condition you might have. However, these conditions will be closely monitored. Other complementary medicines such as herbal preparations, traditional Chinese medicines, natural or homeopathic therapies, or therapies purported to enhance or improve immune system should be avoided.

You must tell us about any procedures or medicines you may be using. This is in your interest as well as important for the study, because they may interact or interfere with *Annona muricata*. You must tell us about any prescription or over-the-counter medications you are taking. You must tell us if you are having other alternative procedures (for example, osteopathy, chiropractic, dietetics, acupuncture). You must also tell us about any changes to these while you are participating in the clinical study. Although interactions with your current medication and the herbal medicine *Annona muricata* are unlikely, there is only limited evidence available.

11 What possible benefits might I get by taking part?

This research will not provide you with any personal benefit. You may benefit from the more frequent review of your condition during the study. By taking part, you may be helping other people in future. Your participation in this research study will contribute to the body of knowledge regarding to the appropriate use of this herb in the overall management and treatment options for people living with cancer. There are

no direct financial benefits to any of the investigator conducting this clinical study. In direct benefit to the investigators include further clinical and academic understanding of the use of *Annona muricata* in people living with cancer.

12 What risks do I run by taking part?

Medical procedures, medicine and tests often have side effects. You may have no side effects, some or all of the side effects listed below. These side effects may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects.

There may also be side effects that the researchers do not expect or do not know about and that may be serious. Tell your study doctor immediately about any new or unusual symptoms that you get.

Many side effects go away shortly after the intervention ends. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your study doctor may need to stop your procedure. Your study doctor will discuss the best way of managing any side effects with you. Some unwanted effects may actually not be related to the study, nevertheless it is important to document these.

The side effects of *Annona muricata* consumption in human were found to be mild, including nausea (13%), heart burn (epigastric pain) (6.6%). A single case of anal pain has also been reported. In animal toxicity studies, there were cases of liver enlargement and injury, movement disorder, lowering of blood sugar and lowering of blood pressure reported. In an observational study in human, movement disorders had also been reported.

This study requires blood sample collection. Collection of blood samples may involve minor discomfort, bruising and rarely a local infection.

The effect of Graviola (*Annona muricata*) on your fertility, including future fertility, may not be known. The effects of Graviola (*Annona muricata*) on the unborn child and on the newborn baby are not known. Because of this, participants must not participate in the research if pregnant, trying to become pregnant, breastfeeding, or planning ovum donation.

If you are female and child-bearing is a possibility, you will be required to undergo a pregnancy test prior to commencing the research project. If you are male, you should not father a child or donate sperm for at least three months after the last dose of study drug.

Both male and female participants must avoid pregnancy during the course of the research and for a period of three months after completion of the research project, as there is potential risk for an abnormal child being born. It is highly recommended that you inform a sexual partner of your participation in the study and the need to avoid pregnancy. The study doctor must discuss effective methods of avoiding pregnancy with you.

[For female participants] If you do become pregnant whilst participating in the research project, you should advise your study doctor immediately. Your study doctor will withdraw you from the research project and advise on further medical attention should this be necessary. You must not continue in the research if you become pregnant.

[For male participants] You should advise your study doctor if you father a child while participating in the research project. Your study doctor will advise on medical attention for your partner should this be necessary.

[For male participants, where appropriate] The study drug may cause harm to a sexual partner through the absorption of the study drug from seminal fluid. The study drug may also affect your sperm risking the

potential for an abnormal child being born. You should discuss with your study doctor effective methods of avoiding this. It is recommended that a condom be worn for all sexual intercourse.

13 How will you use any tissues or samples you take from me?

If you agree to participate in this study, we will collect blood samples as part of your standard care in this clinical study. The collection of blood samples is mandatory. The blood samples will be used for determining and maintaining safety, including monitoring your liver, kidney and immune function. This will be done by a trained experienced hospital staff by inserting a small needle or cannula into the vein of your arm. This helps to monitor for any potential adverse effects of *Annona muricata*. By this close monitoring, adverse events can be minimised, avoided and treated promptly. Further actions can be taken immediately if necessary. Your blood samples will be coded, stored frozen in a secure laboratory freezer at the Concord Hospital ANZAC 3 laboratory, and de-identified. Only pathology staff will be able to access to your blood samples. After all the analyses are completed and the study has been finalised, the samples will be destroyed safely. One standard tube of your blood will be frozen for later analysis, including the potential testing on cancer cell-lines, or analysing the quantity of the bioactive constituents annonacin in the blood samples.

This type of testing is done to further our knowledge about how the study drug works and it will not produce the type of results that will have any useful meaning that would affect your health or treatment.

14 Will you be doing any genetic tests?

There are no genetic tests in this study.

15 What happens if I suffer severe side effects as a result of my participation in this study?

If you suffer any complications as a result of this study, please contact us as soon as possible. In case of an emergency, contact 000.

If, as a result of your participation in this study, you become ill or are injured, immediately advise your study doctor of your condition. In the first instance your study doctor will evaluate your condition and then discuss treatment with both you and your regular treating doctor.

Since you are participating in a non-sponsored study/investigation any question about compensation must initially be directed to your study doctor who should advise their insurer of the matter.

It is the recommendation of the independent ethics committee responsible for the review of this study/investigation that you seek independent legal advice before making any decisions or taking any steps towards compensation for injury.

16 Will you pay me to participate in this study?

You will be reimbursed for reasonable travel and parking expenses.

17 What happens when the study ends?

Four weeks after you finish the treatment, you will be contacted by one of our research team members via telephone to ensure that you have not developed any adverse effects from *Annona muricata*.

18 Could the researchers stop the study early?

Yes, if it does, the study doctor will let you know and explain the reason behind the decision.

In the event of serious adverse events that are judged by the Safety Review Committee to be associated with the study medicine the researchers could stop the study early. Participants would be advised to discontinue the study medicine and will be evaluated by the clinical trial doctor.

19 Will the results of the study be published?

To protect your privacy, no information will be published that could identify you as a participant in this study. The intention of this study is to gather data, however the data will be de-identified. This may take some time and should be discussed with the study doctor. A report of this study may be submitted for publication but individual participants will not be identifiable. You will be made aware of any publication arising from this study. A lay summary of the overall outcome of this study will also be provided to you.

20 Who do I contact if I have a question or complaint?

We have included several contacts for you below. Who you contact depends on what information you need:

For all study enquiries or if you want to talk to the study team at any time:

A business-hours contact for the study team. Ashley Douglas, manager oncology clinical trial, +61 2 9767 6354, Ashley.douglas@health.nsw.gov.au

- If you experience any side effects or complications as a result of this clinical study, you should contact the hospital clinical trial team as soon as possible. They will arrange appropriate medical help.
- 24-hour medical emergency is available by contacting 000 or going to your nearest hospital.
- If you need to talk to the sponsor of this trial, contact: Ashley Douglas, Concord Repatriation General Hospital oncology department, +61 2 9767 6354, Ashley.douglas@health.nsw.gov.au
- If you wish to discuss the study with someone not directly involved, particularly about policies, information or complaints about the conduct of the study or your rights as a participant, you may contact the Human Research Ethics Committee: Jerneen Williams, early phase clinical trials manager jerneenwilliams@bellberry.com.au
- The Bellberry Human Research Ethics Committee has reviewed and approved this study in accordance with the *National Statement on Ethical Conduct in Human Research (2007 – incorporating all updates)*. This Statement has been developed to protect the interests of people who agree to participate in human research studies. Should you wish to discuss the study or view a copy of the Complaint procedure with someone not directly involved, particularly in relation to matters concerning policies, information or complaints about the conduct of the study or your rights as a participant, you may contact the Operations Manager, Bellberry Limited on 08 8361 3222.

21 What do I do if I need to seek compensation for injury?

If you are injured or experience severe side effects, you can take your complaints or requests for compensation to Kate Flinders, Research Governance Manager, 02 9767 5622.

It is the recommendation of the independent ethics committee responsible for the review of this study that you seek independent legal advice before making any decision or taking any steps towards compensation for injury.

22 Insurance

The medical doctors and nurses involved in this study are covered by relevant insurance policy. Doctors are required to have insurance.

23 The consent form

Sign the consent form only after you have made up your mind to take part in this clinical study. If you wish, we will arrange for someone to read the form to you in a language you understand. You must be provided with a signed and dated copy of the participant information and consent form for your personal record.

Consent form

Title	The safety and tolerability of Annona muricata leaf product in people living with cancer: An open-labelled pilot study	
Short title	The Graviola Study	
Protocol number	2022-04-420	
Project sponsor	Sydney Local Health District	
Study doctor	Associate Professor Philip Beale	
Clinical contact person	Associate Professor Philip Beale	+61 2 9767 6354
24-hour medical contact	000	Philip.Beale@health.nsw.gov.au

Note: All parties signing the consent section must date their own signature.

I _____, the undersigned hereby voluntarily consent to my involvement in the research project titled: The safety and tolerability of Annona muricata leaf product in people living with cancer: An open-labelled pilot study

I acknowledge that the nature, purpose and risks of the research project and alternatives to participation have been fully explained to my satisfaction by Dr _____

Specifically, the details of the procedure(s) proposed and the anticipated length of time it will take, the frequency with which the procedure(s) will be performed and an indication of any discomfort that may be expected have been explained to me.

• I freely agree to participate in this research project according to the conditions in the Participant Information Sheet which I confirm has been provided to me.

• I understand that my involvement in this study may not be of any direct benefit to me. • I have been given the opportunity to have a member of my family or another person present while the study is explained to me.

• I have been told that no information regarding my medical history will be divulged to unauthorised third parties and the results of any tests involving me will not be published so as to reveal my identity.

• I understand that access may be required to my medical records for the purpose of this study as well as for quality assurance, auditing and in the event of a serious adverse event and I consent to this access.

• I understand that I am free to withdraw from the study at any stage without prejudice to future treatment. If I decide to withdraw from the study, I agree that the information collected about me up to the point when I withdraw may continue to be processed.

• I am 18 years of age or over.

• I consent to my treating Doctor/s being notified of my participation in this study and of any clinically relevant information noted by the trial doctor in the conduct of the trial.

• I declare that all my questions have been answered to my satisfaction.

• I have read, or have had read to me, and I understand the Participant Information Sheet, version 4, dated July 2022.

Name of study participant:_____

Signature of study participant: _____ Date: _____

Declaration by Principal Investigator (PI) or Co-Investigator (CI): A verbal explanation of the research project, its procedures and risks has been given to the participant and I believe that the participant has understood that explanation.

Name of PI or CI: Signature of PI or CI: _____Date:_____

The Principal Investigator or Co-Investigator must provide the explanation and provision of information concerning the research project.