**Participant Information Sheets and Consent Form**

*Monash Health & the Hudson Institute of Medical Research*

**Title:** Determining the Pharmacokinetics of Oral Creatine in Human Pregnancy

**Multi-stage trial:** Stage 1 of a multi-stage trial

**Project Number:** RES-20-0000-138A

**Project Sponsor:** Monash Health

**Location:** Monash Health, and the Translational Research Facility, Hudson Institute of Medical Research

**Chief Principal Investigator:**
*Dr Kirsten Palmer*. B. Biomed Sci, MBBS (Hons), PhD, FRANZCOG, CMFM. Consultant Obstetrician, Acting head of Maternal Fetal Medicine, Department of Obstetrics and Gynaecology Monash Health, Senior Research Fellow, Monash University, Obstetric Advisor to Consultative Council of Obstetric and Paediatric Morbidity and Mortality.

**Associate Investigators:**
*Dr Stacey Ellery*, B. BioMed Sci, (Hons), PhD, NHMRC Peter Doherty Early Career Fellow,
The Ritchie Centre, Department of Obstetrics and Gynaecology, Monash University.

*Mrs Deborah de Guingand*,
PhD Candidate, RN/RM, BSc, Post-Grad Cert Sexual Health, MPH
The Ritchie Centre, Department of Obstetrics and Gynaecology, Monash University

## Part 1 What does my participation involve?

### 1 Introduction

You are being invited to take part in this research trial because you are a female of reproductive age. You may or may not be pregnant. If you are pregnant with one baby, currently receiving pregnancy care at Monash Health, you may be eligible.

This Participant Information and Consent Form (PI&CF) will tell you about the research trial. It explains the procedures involved. Knowing what is involved will help you decide if you would like to take part in this research project or not.

Please read this information carefully and feel free to ask questions about anything that you do not understand, or if there is more you would like to know about. Before deciding whether or not to take part, you might like to talk about it with a relative, friend or a doctor caring for you.

Participation in this research is voluntary. If you don't wish to take part, you do not have to. If you are pregnant and don't wish to take part your care will not be affected.

If you decide that you would like to take part in the research, you will be asked to sign the consent section. By signing it you are telling us that you:

- understand what you have read;
- consent to participate in the research processes that are described
- consent to collection of information relevant to this research project

You will be given a copy of this participant information and consent form to keep.

## 2 What is the purpose of this research?

Creatine monohydrate is a nutritional supplement that has been available to the public for four decades. It is mostly used by athletes to enhance sporting or training performance; but has been studied in therapeutic trials to assess whether it can improve health outcomes for some diseases.

Creatine supplementation of the mother may protect the baby against a rare but severe event where the baby is deprived of oxygen during pregnancy or in labour. This rare event cannot always be predicted or foreseen. Over the last seven years, we have undertaken research that has shown that creatine supplementation may indeed be an effective treatment.

In the future we may be able to improve outcomes for both mother and baby and reduce the incidence of emergency caesarean sections, if maternal creatine supplementation is found to be effective at increasing creatine delivery to the baby in utero.

This trial aims to find out what dose of creatine monohydrate may be required in pregnancy. To do this we need to give creatine monohydrate in different doses, to women who are pregnant and women who are not pregnant, but of similar age.

Dietary creatine supplementation has been widely studied in females of reproductive age and has an excellent safety profile. However, it has not been trialled in human pregnancy before. Therefore, its use in this research project has to be regarded as 'experimental'.

## 3. Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of *Monash Health*.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2018)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

## 4. What does participation in this research involve?

If you agree to participate in this research trial:

- We will ask you to read this Participant Information Sheet and sign the Consent Form.
- You will receive five grams(g) (5g) of creatine monohydrate in a one-off dose. Your dose of creatine will be delivered to you in 300 mL (just over a cup) of water or fruit juice. You will need to come to either Monash Health or the Hudson Centre for one full day (up to 12 hours) to consume the supplement and allow us to monitor your response.
- We ask that you allow us to insert a peripheral cannula (bung), into your arm, which will remain in place for up to 12 hours and through which, we can collect several blood samples. A cannula (bung) is a short plastic tube that sits inside your vein and allows us to directly take blood without inserting a needle into the vein (venepuncture). You will be free to move around and do other things in between collection of samples.

We ask you to allow us to collect 3 mL blood samples as outlined below.

- The first samples will be required before you have consumed the creatine monohydrate.
- We would then collect a 3 mL blood sample (less than a teaspoon) at each of these intervals: thirty minutes, one hour, one and a half hours, two hours, three, four, six, eight

and ten hours after you have taken the supplement. This will be a total of ten (10) blood collections, over a period of ten (10) hours. No more than 33 mL of blood (approx. 1 1/2 tablespoons) will be taken for research.

- We would collect a urine sample at each of these intervals: baseline and two, four, eight and ten hours. This will be a total of five (5) urine samples, over a period of 10 hours from baseline collection.

In addition to collection of your blood and urine we need your permission for the following:

- To record your vital signs (heart rate, blood pressure, and oxygen levels) before you take the creatine supplement, then at two, four and eight hours after ingestion.
- To collect information on your food consumption up to 4 hours prior to consumption of the drink and allow us to continue to monitor your food and drink intake over the course of the day.
- To allow us to question you about any effects or changes you feel from before consumption, till the end of the trial day and in a phone call the next day.
- To allow us to collect relevant health & other information (age, body mass index, previous pregnancy history if any, current medications).
- <u>For pregnant women only</u>
- To allow us to conduct CTG(cardiotocography) monitoring of your baby's heartbeat, at baseline and again between two-three hours after ingestion.
- To collect relevant information from your Monash Health records with regard to your health, pregnancy, birth and postnatal period.

Final results of the research project will not have any information that could identify you, or any of the other participants, attached to it.

## 5 Do I have to take part in this research project?

No, you don't. Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the research project at any stage.

Your decision whether to take part, or not, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you, or your relationship with Monash Health or the Hudson Institute of Medical Research.

If you decide to take part, you will be given this Participant Information and Consent Form to sign, and subsequently, a signed copy of these documents to keep.

## 6 What are the possible benefits of taking part?

There are no benefits to you or your baby from participation in this trial. However, we hope that the findings from the research project may improve the outcomes for future mothers and babies worldwide if found to be effective.

Where appropriate, we will pay for parking or transport for you, on the day you attend the trial.

## 7 What are the possible risks and disadvantages of taking part?

- The creatine monohydrate used in this trial is a synthetic compound derived from sarcosine and tyrosine, made under strict laboratory conditions, and has been tested for its purity. It is available commercially and marketed as a nutritional supplement. Several studies have used similar or higher doses of creatine monohydrate in females. In this trial, you will be given a total dose of 5g. Previous PK studies have used doses as high as 20g a day with no reported major side effects. It is possible that the drink may cause some gastrointestinal discomfort but these effects, if they occur, are likely to be short in duration and mild in nature. Most placebo-controlled trials have found no difference in effects between women taking placebo compared to those taking creatine supplementation. We believe the doses we are using are unlikely to cause any adverse effects. However, like in any research project, there may be side effects that we do not expect or know about. As such, the researcher will ask you if you experience any change after consuming the supplement. If you experience any unusual symptoms or unwanted effects between questioning, please notify the investigators of the project so it can be recorded and managed appropriately.

- Having a blood sample taken or a cannula (bung) inserted may cause you some discomfort or bruising. Sometimes, the blood vessel may swell, or blood may clot in the blood vessel, or the spot from which tissue is taken could become inflamed. Rarely, there could be a minor infection or bleeding. If this happens, it can be easily treated.

- Pregnant women can be assured, the tissue samples that you are being asked to provide to this research project will not cause you or your baby harm. If you require any other samples to be taken on the day of the trial for clinical care, we will collect these samples alongside the research samples required.

## 8 What will happen to my tissue samples?

The tissue samples provided by you to our research project will be stored and analysed in the laboratories of: The Department of Obstetrics and Gynaecology and the Hudson Institute of Medical Research, both of which are affiliated with Monash University.

The tissue samples you provide will be immediately de-identified at the time of collection and allocated a unique code. This means that any information which could identify you, such as your name, address, date of birth or hospital record number (if applicable) will be removed before your tissue samples go into the laboratory for the scientists to assess the levels of creatine and associated metabolites in your blood and urine.

We expect that all the samples we have collected from you will be needed and used up during the laboratory analysis for this research project. After the scientists have looked at your tissue for this research project, should any tissue(s) remain, we will simply throw it away as clinical waste.

## 9 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, the researchers will tell you about it and discuss this with you to determine whether you wish to continue in the research project. If you decide to continue in the research project you will be asked to sign an updated Consent Form.

It is very unlikely this research project will be stopped unexpectedly but it would be stopped if:

- on receiving new information, researchers might consider it in your best interests to withdraw you from the research project, and this will be subsequently explained to you.
- safety and tolerability events occur that are unexpected or unanticipated
- The governing institution, Monash Health, or the Hudson Institute of Medical Research, make a request for the research project to stop.

## 10 Can I have other treatments during this research project?

It is important to tell the researchers about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell the researchers about any changes to these during your participation in the research project.

## 11 What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team. They will organise for you to sign the Withdrawal of Participation Form. Your withdrawal from this research project will in no way affect your routine clinical care, your relationship with those treating you, or your relationship with Monash Health, Monash University, or the Hudson Institute of Medical Research.

If you do withdraw your consent during the research project, the researchers will not collect any further blood samples or additional personal information from you. Although you should be aware that any tissue samples or personal information that may have already collected will be retained and form part of the research project final results. This is necessary to ensure that the results of the research project can be measured properly and to comply with the law. If you do not want the researchers to do this, you must tell them of this prior to undertaking the research project.

## 12 What happens when the research project ends?

The research project itself will conclude once we have recruited all the pregnant and non-pregnant women, and all stages of the trial and data ('information') collection is complete.

If you would like a summary of the findings from this research project, please inform the named researcher:

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| Name | Ms Deborah de Guingand |

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| Position | PhD Candidate/RN/RM<br>The Ritchie Centre, Hudson Institute of Medical Research and Monash University |
| Telephone | +61 401967646 |
| Email | Deborah.deguingand@hudson.org.au |


## 13 Other relevant information about the research project

The research project has been initiated by the investigators on the team, led by Dr Kirsten Palmer and Dr Stacey Ellery and will be co-ordinated by Ms Deborah de Guingand. Both Dr Palmer and Dr Ellery have internal funding to support this research project. No one from the research team gains financially or has a potential conflict of interest in this research project.

The results of this research will be used by the named researcher Ms Deborah de Guingand as part of her PhD project.

*Additional costs*
There are no additional costs associated with participating in this research project, but we will recompense your time with a payment of transport or your parking fee. The creatine monohydrate, supplied as Creapure®, will be provided to you free of charge.

## 14 What will happen to information about me?

By signing the Consent Form, you consent to the collection and use of your tissue samples and any relevant information about you, that is required for the conduct of this Human Research Ethics Committee (HREC) approved research project.

Any information collected about you will only be disclosed to the researchers who are analysing your samples, with your permission, except as required by law. Any information will always be disclosed to them in a de-identified form, that is without your, for example: name, initials, date of birth, address, telephone number or hospital record number (if applicable) being attached to it.

Any information obtained in connection with this research project that can identify you will remain confidential. This information will be stored in a locked filing cabinet and password-protected database, accessible only by the research team that have been approved by the HREC.

After the research project has been completed, the information will be securely stored for up to seven years by the principal investigator, as currently recommended by the National Health and Medical Research Council (NHMRC) and Monash Health HREC. After this time, all the information will be disposed of in a secure and confidential manner.

In accordance with relevant Australian and Victorian privacy and other relevant laws, you have the right to request access to the information collected and stored by the research team about you. You also have the right to request that any information with which you disagree be corrected. Please contact the research team member named at the end of this document if you would like to access your information.

Your health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities and authorised representatives of the Sponsor, Monash Health or as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant named research personnel and regulatory authorities as noted above.

- Information about your participation in this research project will be recorded in your Monash Health medical records (as applicable).

- It is anticipated that the results from this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission.

## 15 Injury

If you suffer any injuries or complications or require counselling as a result of participating in this research project, you should contact the researchers as soon as possible and you will be assisted with arranging appropriate medical treatment or referral. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian hospital.

## 16 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you would like any further information concerning this research project, or if you have any medical problems which may be related to your involvement in the project, (for example, any side effects) you can contact:

**Chief Principal investigator**:

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| Name | Dr Kirsten Palmer |
| Position | Consultant Obstetrician, Acting Head of Maternal Fetal Medicine, Monash Health and Senior Research Fellow, Department of Obstetrics and Gynaecology, Monash University |
| Telephone | +61 3 9594 6666 |
| Email | Kirsten.palmer@monash.edu |

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

**Reviewing HREC approving this research and HREC Executive Officer details:**

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| Reviewing HREC name | Monash Health, Human Research Ethics Committee (HREC) |
| HREC Executive Officer | Mrs Deborah Dell<br>Manager, Human Research Ethics Committee and Manager, Research Support Services, Monash Health. |
| Telephone | +61 3 9594 4605 |
| Email | *deborah.dell@monashhealth.org* |

**Local HREC office contact (Single Site -Research Governance Officer):**

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|---|---|
| Name | Mr Michael Kios |
| Position | Research Governance Officer |
| Telephone | +61 3 9594 4606 |
| Email | michael.kios@monashhealth.org |

**Consent Form**

*Monash Health & the Hudson Institute of Medical Research*

**Title**: Determining the Pharmacokinetics of Oral Creatine in Human Pregnancy
**Project Number:** RES-20-0000-138A
**Project Sponsor:** Monash Health
**Location:** Monash Health & and the Translational Research Facility, Hudson Institute of Medical Research

**Chief Principal Investigator:**
*Dr Kirsten Palmer*. Acting Head of Amber Maternity Team and Obstetrician, Monash Health, Senior Research Fellow, Monash University, Obstetric Advisor, Consultative Council of Obstetric and Paediatric Morbidity and Mortality

**Declaration by Participant**

- I have read the Participant Information Sheet or someone has read it to me in a language that I understand.
- I understand the purposes, procedures and risks of the research described in the project.
- I have had an opportunity to ask questions and I am satisfied with the answers I have received.
- I freely agree to participate in this research project as described and I understand that I am free to withdraw at any time during the research project without it affecting my future health care.
- I understand that I will be given a signed copy of this document to keep.

Name of participant (Please PRINT):

Signature: Date: Time:

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**Declaration by senior researcher†**
I have given a verbal explanation of the research project; its procedures and risks and I believe that the participant has understood that explanation.

Name of the senior researcher (Please PRINT):

Signature: Date: Time:

† A senior member of the research team must provide the explanation of, and information concerning, the research project.
Note: All parties signing the consent section must date their own signature

**Form for Withdrawal of Participation**

**Title:** Determining the Pharmacokinetics of Oral Creatine in Human Pregnancy

| | |
|---|---|
| **Project Number** | RES-20-0000-138A |
| **Project Sponsor** | Monash Health |
| **Location** | Monash Health and the Translational Research Facility, Hudson Institute of Medical Research |
| **Lead Principal Investigator** | Dr Kirsten Palmer |

**Declaration by Participant**

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with Monash Health or Hudson Institute of Medical Research.

Name of Participant (please PRINT):

Signature: Date: Time:

*If the participant's decision to withdraw is communicated verbally, the researcher will need to provide a description of the circumstances below.*

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**Declaration by the senior researcher†**

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

Name of the senior researcher (Please PRINT):

Signature: Date: Time:

† A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project.

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