PARTICIPANT INFORMATION STATEMENT AND CONSENT FORM

The ENHANCE study
Can a daily supplement improve egg quality?

The effects of NR (Nicotinamide riboside) supplementation on the egg quality of women of advanced age undergoing IVF: a randomised placebo-controlled double-blind proof of concept clinical trial

The purpose of this study is to find out whether a diet supplement (NR) might improve egg quality in IVF treatment.

1. What is the research study about?

You are invited to take part in this research study. The research study aims to evaluate the use of a dietary supplement called nicotinamide riboside (NR). In this study, we plan to investigate the use of NR at two different dosages compared to dummy capsules (placebo). If you join, we will ask you to take 250mg, 1000mg, or dummy capsules once a day for six weeks up to the IVF egg collection. The embryos will be frozen and transferred in the next cycle (within at least 30 days after the last capsule intake). The study will help us understand whether the supplement might improve egg quality in IVF treatment.

2. Who is conducting this research?

The study is being carried out by the following researchers:

Professor William Ledger: Chief Investigator, Director of Reproductive Medicine at The Royal Hospital for Women, Fertility and Research Centre (FRC) and Professor of Obstetrics and Gynaecology, UNSW Medicine

Dr Rachael Rodgers, Deputy Director of Reproductive Medicine at The Royal Hospital for Women, Fertility and Research Centre (FRC) and Fertility Specialist at Genea, Sydney.

Professor Robert Gilchrist: NHMRC Senior Research Fellow, Head, Oocyte Biology Research Unit, Discipline of Obstetrics & Gynaecology, UNSW Sydney

Dr Lindsay Wu: Senior Research Fellow, School of Medical Sciences, UNSW Sydney

Dr Angelique Riepsamen: Post-Doctoral Research Fellow, School of Women's & Children's Health UNSW Sydney

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Dr Michael Costello: Clinical Academic at Fertility & Research Centre, at The Royal Hospital for Women, UNSW Medicine

Dr Ionara Barcelos: Research Associate and Fertility Specialist Visiting Fellow at The Royal Hospital for Women, Fertility and Research Centre (FRC) & School of Women's & Children's Health UNSW Medicine

Mrs Prudence Sweeten: Clinical Fertility Research Nurse, Discipline of Obstetrics & Gynaecology& School of Women's & Children's Health UNSW Medicine, Clinical Nurse at Fertility and Research Centre (FRC)

The study will be supported by the University of New South Wales. ChromaDex, the manufacturer of NR, will provide medication for the trial at no cost to UNSW but will not give any financial support.

3. Do I have to take part in this research study?

Participation in this research study is entirely voluntary. Our study will assess if the use of this supplement improves egg quality in women from 36 to 42 years of age. Hence, you are being invited to take part in this study because you are over 36 years of age and planning an IVF cycle. If you do not want to take part, you do not have to. If you do decide to participate and later change your mind, you are free to withdraw from the study at any stage.

If you decide you would like to participate in the research study, you will be asked to:

- Read the information carefully and ask questions if necessary
- Sign and return the consent form
- Take a copy of this form to keep.

4. What does participation in this research require?

If you agree to participate you will be asked to complete the following research procedures:

Screening:

A research staff member will assess your eligibility to participate. The screening process will be done in person and will take no longer than 5 minutes to complete. The clinical research nurse and your treating doctor will also have access to your medical history which will help to determine if you are eligible.

If you are eligible, then you will be asked to join the research project. If not, your IVF treatment will continue as part of routine care.

Randomisation: The aim of the research is to compare the outcomes of the use of NR at the dosage of 250mg or 1000mg, once a day for six weeks before an IVF cycle, with the use of dummy capsules, which are made of microcrystalline cellulose, an inert filler, which is white in colour and is a non-reactive substance. To ensure you have an equal chance of being placed in any of the groups, a computer will allocate you randomly into a group, like the flip of a coin. You will not know which group you will be assigned to. Once randomised, you will be allocated to one of the following groups and take four capsules per day.

Intervention 1	Intervention 2	Control
NR: 250mg (1 NR capsule + 3 dummy capsules)	NR: 1000mg (4 NR capsules)	Placebo (4 dummy capsules)

Sample Collection: There will be no more blood tests other than those required for clinical management in this trial. We will collect an extra 15mL (1 tablespoon) of blood only on occasions when a sample is needed for routine clinical monitoring, which means you will NOT need an additional blood test. All blood samples collected will be analysed for the purpose of this research and will be destroyed following analysis. There is no additional procedure or visits involved in this study.

From the blood sample provided, we will be collecting data on your hormonal levels. Follicular fluid will be collected at the time of egg collection, and we will be analysing hormonal levels and the levels of the supplement taken in the follicular fluid. We will also collect personal and clinical data from your medical record such as age, weight and habits (such as smoking), as well as data on the quality of your eggs obtained through the analysis of a single photograph of your eggs obtained at the time of fertilisation. We will be also collecting data (from your medical records) of number of eggs collected, embryos surviving to day 3 and blastocysts (embryos surviving to day 5). Should you become pregnant after the embryo transfer, we will be collecting data on your pregnancy outcomes, such as the weight and health of your child at birth.

Intervention: NR is widely used as an anti-aging treatment without prescription recognised as safe by the TGA (Therapeutic Goods Administration) in the dose of 300mg once a day. NR increases NAD levels in the bloodstream. NAD may improve the quality and number of eggs in an IVF cycle. Experiments in mice have shown improvement in egg quality and fertility, but this has not been tested in humans undergoing IVF. In this study, each participant will take the medication (250, 1000mg or placebo) once a day for **six weeks in total**: four weeks before the ovarian stimulation process begins, then during ovarian stimulation for approximately two weeks, up to the day of the trigger injection, which is administered 36 hours before the IVF surgery. You should take the tablets during the morning with or without food. If you forget to take the tablet within 12 hours, you should take it. If you forget, and remember after this period, you should skip the dose and take the tablet in the next morning. After the egg collection, the embryos will be frozen and transferred in the next cycle (within at least 30 days after the last capsule intake).

Medical Drugs: Nicotinamide riboside chloride is approved as a food supplement (non-prescription) in Australia and will be used in this research. NR may have benefits, such as:

Maintain or support energy levels, general health and wellbeing;

Help convert nutrients into energy;

Support body and tissue repair regeneration;

Promote increase NAD+ levels and help prevent NAD+ deficiency in the body;

Help the synthesis of vitamins in the body.

NR is not an approved treatment for improving fertility outcomes in IVF patients in Australia, and it has not been reviewed for effectiveness. Therefore, we plan to investigate to see if it improves the quality of eggs collected in an IVF cycle.

Nicotinamide riboside is not recommended for use by pregnant and breastfeeding women.

Additional Costs and Reimbursement: There are no additional costs involved, nor will you be paid for participating in the study.

5. What are the risks involved?

Medical treatments often cause side effects. It is documented that NR may cause nausea, hot flushes, fatigue, headaches, diarrhoea, stomach discomfort and indigestion. You may have none, some or all the effects listed, and they 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 be side effects that the researchers do not expect or do not know about, which may be serious. Tell the research team immediately about any new or unusual symptoms. Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long-lasting, or permanent. The research group believes this would be a rare event because previous research projects with humans using a higher dose of the supplement reported no severe side effects.

If a severe side effect or reaction occurs, your study doctor might need to stop your treatment. The research team will discuss the best way of managing any side effects with you.

6. What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research. Your participation will provide valuable information to help other IVF patients.

7. What are the alternatives to taking part in the research?

Participation in this study is entirely voluntary. It is up to you whether you participate. If you decide not to participate, you will continue to receive your routine IVF treatments as before. Your decision not to participate will not affect your relationship with the Fertility and Research Centre (FRC), your treating doctor, or the staff caring for you now or in the future.

8. What will happen to information about me?

All data and sample collection that includes information about your identity will be collected and stored securely. This procedure is done to protect your confidentiality. Information collected from you for the purpose of this clinical trial will be stored at the FRC. The data collected will not be used for secondary or future research purposes.

The clinical research team will have access to your medical records in order to review your IVF treatment cycle details. This will allow us to record the results of the study treatment. If you conceive a pregnancy following this treatment, we will contact you during the pregnancy and follow up after the birth of your baby.

Only the research team will have access to the key that links the information back to your identity. A copy of this data will not identify you in any way.

All information collected for this research will be retained for a minimum of 15 years after the date of publication. The information is personal information for the purposes of the Privacy and Personal Information Protection Act 1998 (NSW). You have the right of access to personal information held about you, the right to request correction and amendment of it, and the right to make a complaint about a breach of the Information Protection Principles, as contained in the PPIP Act.

It is anticipated that the results from this research project will be published in academic journals and presented at Reproductive Endocrinology and Infertility conferences. In any publication or presentation, data will be provided so that your personal information cannot be identified.

9. Can I find out what the results of the research study are?

The research team will publish the results in scientific literature and report the results of the research. All information will be published in a way that will not identify you. Copies of our publications of this research will be available at the Fertility and Research Centre.

10. What if I want to withdraw from the research study?

If you do consent to participate, you may withdraw at any time. You can do so by completing the 'Withdrawal of Consent Form', which is provided at the end of this document, or you can phone the research team and tell them you no longer wish to participate. Your decision not to participate or to withdraw from the study will not affect your relationship with the FRC. If you decide to leave the research study, the researchers will not collect additional information from you. You can request that any identifiable information about you be withdrawn from the research project.

11. What if I have a complaint or any concerns about the research study, and will I receive compensation if suffer any injuries or have complications?

If you suffer any injuries or complications because of this research project, you should contact the study team as soon as possible, and you will be assisted with arranging appropriate medical treatment. 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 public hospital.

Complaints Contact

If you have a complaint regarding any aspect of the study or the way it is being conducted, please contact the SESLHD Human Ethics Coordinator:

Position	**SESLHD Human Research Ethics Committee**
Telephone	+ 61 2 9382 2458
Email	SESLHD-RSO@health.nsw.gov.au
HC Reference Number	*To be inserted after approval*

Position	**UNSW Clinical Trial Sponsor, Dr Ted Rohr UNSW Clinical Trial Sponsor's Delegate, Research Ethics Compliance Support**
Telephone	02) 93856222
Email	humanethics@unsw.edu.au
HC Reference Number	*To be inserted after approval*

12. What should I do if I have further questions about my involvement in the research study?

The person you may need to contact will depend on the nature of your query. If you require further information regarding this study, or if you have any issues which may be related to your involvement in the study, please contact the following member/s of the research team:

Research Team Contact Details

Name	**Dr Ionara Barcelos**
Position	Research Associate - Fertility Specialist/Visiting Fellow
Telephone	(02) 9382 6727 **Email:** ionarabarcelos@hotmail.com

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Name	**Prudence Sweeten**
Position	Clinical Fertility Research Nurse
Telephone	(02) 9382 6515 **Email:** p.sweeten@unsw.edu.au
Name	**Professor William Ledger**
Position	Principal Investigator
Telephone	(02) 9382 6515 **Email:** w.ledger@unsw.edu.au

CONSENT FORM – PARTICIPANT PROVIDING OWN CONSENT

Declaration by the participant

- ☐ I understand I am being asked to provide consent to participate in this research study.
- ☐ I have read the Participant Information Sheet, or someone has read it to me in a language that I understand.
- ☐ I understand the purposes, study tasks and risks of the research described in the study.
- ☐ I provide my consent for the information collected about me to be used for the purpose of this research study only.
- ☐ 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 study as described and understand that I am free to withdraw at any time during the study and withdrawal will not affect my relationship with any of the named organisations and/or research team members.
- ☐ I understand that I will be given a signed copy of this document to keep.
- ☐ I understand that the results of the research will be made available at the FRC.

PARTICIPANT SIGNATURE

Name of Participant	
Signature of Participant	x
Date	

Declaration by Researcher*

☐ I have given a verbal explanation of the research study; its study activities and risks and I believe that the participant has understood that explanation.

Researcher Signature*

Name of Researcher	
Signature of Researcher	
Date	

+An appropriately qualified member of the research team must provide the explanation of, and information concerning the research study. All parties signing the consent section must date their own signature.

FORM FOR WITHDRAWAL OF PARTICIPATION

I wish to **WITHDRAW** my consent to participate in this research study described above and understand that such withdrawal **WILL NOT** affect my relationship with FRC.

☐ I am withdrawing my consent and I would like any identifiable information collected about me which I have provided for the purpose of this research study withdrawn.

☐ I am withdrawing my consent to participate in further components of this research and provide my permission for the research team to retain and/or use information collected about me which I have provided for the purpose of this research.

☐ I am withdrawing my consent, and I understand that any information already published and/or not linked to my identity cannot be withdrawn from the research.

☐

Participant Signature

Name of Participant (please print)	
Signature of Participant	x
Date	

The section for Withdrawal of Participation should be forwarded to:

CI Name:	Professor William Ledger
Email:	w.ledger@unsw.edu.au
Phone:	(02) 9382 6515
Postal Address:	Level 1, Royal Hospital for Women Barker Street, RANDWICK NSW 2031