UCL COMPREHENSIVE CLINICAL TRIALS UNIT

NAMinG

TO BE PRESENTED ON LOCAL HEADED PAPER

Trial Title: Nicotinamide in Glaucoma (NAMinG): A randomised, placebo-controlled, multi-centre, Phase III trial

Participant Information Sheet

We are inviting you to take part in a research trial. You have been given this information sheet because your doctor feels you may be suitable to take part.

Before you decide if you would like to take part, it is important for you to understand why the research is being done and what it will involve.

1. What is the purpose of this trial?

Glaucoma is an eye condition in which the optic nerve (nerve of sight) becomes damaged. This damage has no symptoms in its early stages. If untreated, the vision loss in most patients gradually gets worse and may become noticeable or even severe. The damage is not reversible, so the aim of treatment is to slow down or stop the damage. Standard treatments aim to lower the pressure inside the eye with eye drops or laser therapy. Some people with glaucoma, however, continue to lose vision despite standard treatment.

The aim of this trial is to find out whether taking high doses of vitamin B3 (also known as Nicotinamide or NAM), when used with standard treatment for lowering pressure in the eye, can reduce the amount of sight loss in people with recently diagnosed glaucoma. We will also try to identify which people with glaucoma are likely to benefit most from high dose NAM and evaluate its long-term safety.

Recent research has looked at parts of cells called 'mitochondria' which produce most of the energy for cells to function normally. Nerve cells in the eye need a lot of energy to function and survive. The research has shown that some people with glaucoma have mitochondria which function less well than normal. Evidence so far has shown that mitochondrial function can be improved with NAM treatment.

This trial will also help us to identify tests which might predict the people most at risk of glaucoma worsening and who respond best to each type of treatment through two optional sub-studies that you may be able to take part in. Ultimately, this will allow us to 'personalise' glaucoma treatment.

We aim to recruit 496 patients to this trial from several hospitals across the UK.

2. Why am I being asked to take part?

You are over 18 and have been diagnosed with open-angle glaucoma (OAG) within the last 12 months.

3. Do I have to take part?

No. It is up to you to decide whether you want to join the trial. Your participation in the trial is completely voluntary and will not affect the standard of care you receive.

Not everyone will be able to take part in this trial. Only patients who meet all the trial entry requirements and are willing to participate may take part. Your trial doctor will assess your eligibility.

If you would like to participate, a member of the research team (your nurse or doctor) will discuss this information sheet with you. You will have the opportunity to ask any questions you may have and will be asked to sign the consent form for this trial. You will be given a copy of the signed consent form and this information sheet to keep.

If you agree to participate in this trial, you will not be able to participate in any other drug trials at the same time. Also, you must not have been involved in any previous clinical trial for your glaucoma.

4. What do I need to know about the medicines in this trial?

In this trial there will be **two** treatment groups:

A) Nicotinamide (NAM; the **ACTIVE** medication) and

B) Placebo or *'dummy'* (NO ACTIVE medication).

You will be asked to take either Nicotinamide tablets **OR** placebo (dummy) tablets. You will not know to which group you have been assigned until the trial has finished.

Nicotinamide (NAM) is a form of vitamin B that is used by your body to help turn food into energy and is important for the development and function of healthy cells. It is present naturally in many foods, and in dietary supplements, at much lower doses. The high dose in this trial has been used before and was found to be well-tolerated.

The **Placebo (dummy)** tablet **does not contain any active ingredients** but will look exactly like the active medication.

5. Which treatment group will I be in?

To find out if NAM is an effective treatment for glaucoma, we need to compare a treatment group of participants taking NAM with a treatment group not taking NAM. We will put participants into 2 groups, so that half receive the active NAM and half receive placebo (dummy) treatment. Participants will be 'randomly' allocated to a treatment group using a computer system (similar to tossing a coin). This process is called 'randomisation'. This means you will not be able to choose your group and you will not know which group you are in, until after the trial has finished.

Neither you nor your doctor or nurse will be told which treatment has been allocated to you (although if your doctor needs to find out they can do so).

6. What will I need to do if I take part?

If you wish to take part, your doctor or nurse will assess you to make sure that you are suitable for this trial. You will be asked some questions about your condition and, if suitable, you will undergo further eye assessments and blood tests.

Your participation in the trial will be for up to 30 months. However, the trial overall will last for 5 years from beginning to end. Most of the clinic visits during the trial will be in line with normal scheduled hospital appointments; you will be asked to attend eight (8) hospital visits in total over 30 months, about three (3) more than you would if you were not participating in the trial. You will also receive at least four (4) telephone calls over the 30-month period.

You will receive treatment to reduce the pressure in your eye, as you would for standard glaucoma care. According to your preference, this will be either eye drops and/or non-invasive laser treatment (known as 'selective laser trabeculoplasty' (SLT)).

Your General Practitioner (GP) will be sent a letter with a copy of this information sheet to inform them of your participation in this trial.

What will happen to me during the trial?

Screening Visit

During this visit, the trial doctor or nurse will ask you for information about your medical history and any medications that you are taking. This trial aims to be as close to normal 'real-world' glaucoma care as possible, so you will have an eye examination, eye pressure tests, a test to measure how easily you can see spots of light across your field of vision (called a 'visual field test'), and a scan of the back of your eye (called 'Optical Coherence Tomography' or OCT). These are routinely performed for all glaucoma patients.

All tests will be non-invasive and discomfort will be minimal. At some visits, drops to dilate your pupils may be used to help us examine the back of your eye more closely. Some of the test results will be provided to an image grading centre located at Moorfields Eye Hospital, known as the Moorfields Reading Centre, to help confirm your eligibility for the trial. Subsequent OCT scans and visual field test results will be provided to the Moorfields Reading Centre to enable us to evaluate whether NAM treatment is helpful.

Your blood pressure will also be measured, and blood samples will be taken to check your liver function, kidney function, sugar levels and levels of vitamin B3.

Once these blood samples have been analysed, any remaining excess will be disposed of as per your hospital's local policy.

The assessments and tests will be the same for both treatment groups throughout the trial duration and will take an hour and a half for most patients, but no more than 2 hours in total.

We do not know if NAM can affect an unborn child and so pregnancy will mean you cannot take part in the trial. If you are a woman of childbearing potential (pre-menopausal and not sterilised), urine samples will be taken to check if you are pregnant. Once the urine sample has been analysed, the sample will be disposed of as per your hospital's local policy. **A urine sample for women of childbearing potential will be repeated at all visits, and then 30 days after finishing trial treatment, at which point the pregnancy test kit will be posted to your home. (See section 7below).**

Baseline Visit

You will return for your Baseline Visit (Visit 1), which will be between 2 weeks and 3 months after your Screening Visit. Your weight, height and blood pressure will be measured. You will be asked to fill in questionnaires about your general health, your diet and your vision.

You will then be randomly allocated by computer to one of the treatment groups (NAM or placebo).

Both groups will take either NAM or placebo by mouth twice a day (to be taken with food), or as instructed by your trial doctor:

- For the **first 6 weeks** you will take **one tablet twice a day; morning and night** (this is 1.5g a day for participants randomised to the NAM group).
- From **Week 7 onwards** until the end of the trial (Month 27) you will take **two tablets twice a day; morning and night** (this is 3.0g a day for participants randomised to the NAM group).

You will be provided with a paper diary and asked to record information about your trial medication intake, any missed doses and side effects that you may experience. You will be asked to bring all your trial medication bottles, used and

unused, to each of the hospital trial visits. The research team will review the amount of medication taken and the information you recorded in your diary.

Towards the end of the first 6 weeks of taking your medication and **before** you increase the number of tablets you take, your trial doctor or nurse will phone you to remind you to increase your dose, ask how you are getting on, and whether you have experienced any side effects.

Other Trial Visits

Your second visit **(Visit 2)** will be three months later, and after that, every six months until Visit 6. **Your final visit will be Visit 7 (Month 27)** and will happen three months after Visit 6. Then you will stop taking the trial medication.

You will receive further supplies of your trial medication at Visits 3, 4, 5 and Visit 6.

For further information on assessments and visits, please refer to the trial summary at the end of this document.

During the trial, if your eye pressure is not controlled or your vision becomes worse, you and your doctor will decide whether you will be given either more laser treatment or more (different) eye-drops, just as you would if you were not in this trial.

7. What are the side effects of the trial medications?

In any clinical trial, there is a chance of experiencing side-effects from the trial medications. Research has shown NAM is well-tolerated at the high dose given in this trial and the known side effects have been listed below.

If you experience any unpleasant side effects, whether listed below or not, you should report them to the research team at your next hospital trial visit or during one of the phone calls.

If you take part, you will be given a Participant Trial Card to carry at all times, saying you are part of this trial. If you experience any side effects, you can show this to the doctors before they give you any treatment.

The possible (including very rare) side effects of Nicotinamide (NAM) are:

- Flushing, redness, itching and rash of skin
- Gastro-intestinal symptoms such as sore mouth, heartburn, vomiting, nausea, diarrhoea, flatulence
- Headache, dizziness
- Liver function test abnormalities, jaundice
- Eye symptoms, such as blurred or disturbed vision, blood in the front part of the eye (hyphaema) and swollen eyelids (periorbital oedema)
- Fatigue
- Alopecia
- Heart palpitations
- Poorly controlled blood sugar levels

Interactions with other medications: There are some medications that can cause side-effects when taken with NAM. You should take all your medications, including dietary supplements, with you to your Screening Visit. The research team will review your medication at each visit. It is important to tell your trial doctor about all your medications (prescribed and over the counter) that you are taking before starting the trial and throughout the duration of the trial.

The following medications are not permitted to be taken during your participation in this trial:

Isoniazid and/or Pyrazinamide: If you are taking these medication you will not be able to take part in the trial as they may lower levels of vitamin B3 in the body.

Carbamazepine, Phenobarbital and/or Primidone: If you are taking these medication you will not be able to take part in the trial as there is a possible interaction with nicotinamide.

Vitamin B3 supplements: You cannot take any additional B3 (including skin preparations such as ointments/emulsions) at the same time as participating in this trial as higher doses than prescribed (more than 3.0g a day) may cause side effects, including liver damage.

Ginkgo Biloba and / or Coenzyme Q10 (CoQ10) supplements: You cannot take Ginkgo Biloba and/or Coenzyme Q10 supplements at the same time as participating in this trial as these may interfere with the effect of NAM.

In addition, if a course of **Tetracyclines** (antibiotic used to treat some infections) is prescribed during your participation on the trial, you should inform the research team immediately as your trial medication will need to be temporarily stopped until your course of tetracyclines is complete.

Avoiding pregnancy: We do not know if NAM is a risk for a pregnant woman, an unborn baby, or a breastfeeding child. Therefore, pregnant and breastfeeding women (as well as women planning to become pregnant) are not allowed to take part in this trial. We will ask you to take highly effective contraceptive precautions during the trial and for 30 days after your last trial medication. If you are a male participant, you will be advised to use adequate contraception for the duration of the trial and for 30 days after your last trial medication. You can discuss the type of adequate contraception with your trial doctor/nurse. **If a pregnancy does occur, you must tell your trial doctor immediately**.

8. What are the possible disadvantages or risks of taking part?

All medical procedures involve some risk, but this is usually low. It is possible that there could be risks associated with this trial that we do not know of yet. Information on the most common or serious side-effects of procedures carried out in this trial is listed below. If you have questions about side-effects or risks, please ask your trial doctor.

Blood samples: The collection of blood samples can be uncomfortable, but rarely results in any serious problems. Reported side effects include feeling light-headed or faint, bruising and/or discomfort around the needle site. Every effort will be made to minimise this. Blood samples will be taken at Screening, Visits 2 and 5. The volume of blood collected will be up to 15mls (about 3 teaspoons).

Other risks: All efforts are made to make this trial safe. Despite this, some risks might not be possible to predict.

9. What are the possible benefits of taking part in the main trial?

Not all patients will receive NAM and, if you do take part in this trial, we cannot guarantee that it will benefit you. However, the information we get from this trial will help us find out if NAM provides better outcomes for people with glaucoma and therefore, will improve treatment for all glaucoma patients in the future.

10.Optional sub-studies

This trial includes two optional sub-studies, and the research staff will tell you about this. Please refer to the separate information sheets for more information. If you decide not to take part, this will not affect your participation in the main trial and the care you receive.

11.What will happen when the trial ends?

As nicotinamide 750mg tablets are not licensed medicine in the UK, nicotinamide treatment will not be available to any participant after the trial has ended, however it is widely available as a food supplement, taken at lower dosages. A positive result from the trial would motivate manufacturers to produce the drug at higher doses, and patients could purchase the recommended dose. In the meantime, you will continue to receive your routine standard of care treatment for Glaucoma and routine appointments with your treating doctor and GP.

12. More information about the trial

Will I be paid?

You will not be paid for taking part in this trial, however, travel costs you incur for attending the three additional trial visits (Screening, Visit 2 and Visit 7) will be reimbursed up to £30 for each visit. Please keep all relevant receipts as you need to provide these to the research team at your hospital.

How will we use information about you?

We will use information from you and your medical records for this research project.

This information will include your name, NHS number, date of birth and contact details, which will be held by the Hospital. People will use this information to do the research or to check your records to make sure that the research is being done properly. If you are not contactable, researchers will access your medical records via NHS Digital (The Spine) to obtain your contact details.

The people who do no need to know who you are will not be able to see your name, NHS number or contact details. Your data will have a coded number instead. We will keep all information about you safe and secure.

Where there is a possibility that your information may be sent outside the UK for regulatory or research purposes, the country it is sent to must follow our rules about keeping your information safe.

University College London (UCL) is the Sponsor for this trial, based in the United Kingdom, and has delegated some of their responsibilities as Sponsor to the Comprehensive Clinical Trials Unit (CCTU) at UCL. UCL CCTU will be using information from you and your medical records in order to undertake this trial and they will act as the 'data controller'. This means that we are responsible for looking after your information and using it appropriately under the provisions of the UK Data Protection Act 2018.

Certain individuals from CCTU and regulatory organisations may look at your medical and research records to check the accuracy of adherence to the trial protocol and data recording. The CCTU will only receive pseudonymised information which will be stored in the trial database hosted by 'OpenClinica'.

To safeguard your rights, we will use the minimum personal identifiable information i.e. partial date of birth along with your coded number (Participant Identification Number; PIN). The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.

We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Once we have finished the study, we will keep the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

UCL CCTU will store securely identifiable information about you from this trial for 5 years after the trial has finished. The CCTU is registered under the UK Data Protection Act (DPA) to store this information. There is a question about this on the consent form that we will ask you to sign before you begin the trial.

If you agree to take part in this study, you will have the option to take part in future research using your data saved from this study, for which we will obtain your consent. With your permission, your data collected during the trial may be used for future ethically approved research, either at academic sites nationally or internationally, or in academic collaborations with commercial partners. Data may be transferred both within and outside the European Economic Area as part of ongoing and/or future research. This may include combining data with those of other patients in other trials in order to understand important factors related to glaucoma. The country(s) to which the data are sent must follow our rules about keeping information safe. Data will only be shared among approved researchers and such data will always be pseudonymised, so you are not identifiable.

With your consent, we would also like to use your routinely collected clinical data for long-term assessment of the impact of NAM on visual function after the end of the trial.

You can find out more about how we use your information here:

- https://www.ucl.ac.uk/data-protection/policies/2022/jan/data-protection-policy
- at www.hra.nhs.uk/information-about-patients/
- by asking one of the research team
- by sending an email to the UCL Data Protection Officer on data-protection@ucl.ac.uk
- by contacting cctu-enquiries@ucl.ac.uk
- at www.ucl.ac.uk/cctu/use-of-data
- HRA Link for further information: https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/data-protection-and-information-governance/gdpr-guidance/templates/template-wording-for-generic-information-document/
- https://www.openclinica.com/privacy-policy/
- https://www.sealedenvelope.com/privacy/

To read UCL's Participants in health and care research privacy notice, please follow this link: https://www.ucl.ac.uk/legal-services/privacy/participants-health-and-care-research-privacy-notice

What will happen if I don't want to carry on with the trial?

You are free to withdraw from the trial at any time, without giving any reason. The standard of your care will not be affected. We will keep the information that we have already collected, to use in the analysis of the trial results.

If you wish to stop taking the trial medication ONLY but are happy to continue to be followed up, we will ask you to attend the remaining trial visits. Information collected may still be used for the trial.

What will happen to the results of the research?

When the trial is completed, we will be able to provide you with a summary of the results on request. The summary will be published on the UCL CCTU website at https://www.ucl.ac.uk/cctu and via glaucoma patient networks. The researchers will share the trial data on an openly accessible website and in medical journals. Your identity and personal details will be kept confidential. No named information will be published about you on any websites or in any reports.

Who is organising and funding the trial?

This trial is organised by the Comprehensive Clinical Trials Unit (CCTU) at University College London (UCL). The trial coordination, data collection from the participating hospitals, analysis and administration will be provided by the CCTU at UCL. You can find out more about us at https://www.ucl.ac.uk/cctu.

This trial is funded by the National Institute for Health and Care Research Efficacy and Mechanism Evaluation (NIHR-EME) Programme (Grant Reference Number 132758). The CCTU is independent of the NIHR-EME.

Your doctor is not receiving any money or other payment for asking you to take part in the trial.

Who has reviewed the research?

This trial has been reviewed and authorised by the Medicines for Healthcare Products Regulatory Agency (MHRA) as well as an NHS Research Ethics Committee (East Midlands – Leicester South REC), the Health Research Authority (HRA) and the Research and Development office at your participating hospital.

What if relevant new information becomes available?

During a trial, new information sometimes becomes available about the medicines that are being studied. If this happens, your doctor will discuss with

you whether you want to continue in the trial. If you decide to stop taking part, your doctor will arrange for your care to continue outside of the trial.

Your doctor might also suggest that it is in your best interests to stop taking part and will explain the reasons and arrange for your care to continue outside of the trial. If you decide to continue in the trial, you will be asked to sign an updated consent form.

What happens if the trial stops early?

Very occasionally, a trial is stopped early. If this happens the reasons will be explained to you and your normal glaucoma care will continue.

What if something goes wrong for me?

Every care will be taken in the course of this trial. However, in the unlikely event that you're injured or, for female participants during your pregnancy, your unborn child is injured by taking part, compensation may be available.

If you suspect that the injury is the result of the Sponsor's (University College London) or the hospital's negligence, then you may be able to claim compensation. After discussing with your trial doctor, please make the claim in writing to Professor David Garway-Heath, who is the Chief Investigator for this trial and is based at University College London Institute of Ophthalmology. The Chief Investigator will then pass the claim to the Sponsor and on to the Sponsor's Insurers. If you have a claim, then it might be helpful to consult a lawyer.

You may also be able to claim compensation for injury caused by participation in this trial without the need to prove negligence on the part of the University College London or another party. You should discuss this possibility with your trial doctor in the same way as above.

Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated by members of staff or about any side effects (adverse events) you may have experienced due to your participation in the trial, the normal National Health Service complaints mechanisms are available to you.

Please ask your trial doctor if you would like more information on this. Details can be obtained from the NHS website.

Alternatively, you can contact the Patient and Advice and Liaison Service at the hospital:

[Insert address and telephone number of local PALS department]

13.Contact for further information

If you have any further questions about this trial, please contact the local research team:

During office hours (9am - 5pm):

[Insert trial doctor details:]

[Insert email:]

[Insert telephone:]

[Insert research nurse details:]

[Insert email:]

[Insert telephone:]

Emergency out-of-office hours telephone no: [Insert]

If you decide you would like to take part, please read and sign the consent form. You will be given a copy of this information sheet and of the consent form to keep. A copy of the signed consent form will also be filed in your patient medical notes and one will be filed with your trial records.

Thank you for taking the time to read this information sheet and to consider the trial

NAMinG Trial – Summary of Visits and Assessments

Screening Visit

- Discuss trial with doctor and sign consent form
- Review of medication, BP measurements, eye examination/eye test, and blood tests
- Urine pregnancy test for women of child bearing potential

Receive NHS Standard of Care IOP-Lowering Treatment (eye drops or laser)

Visit 1

- Review of medication, BP and weight measurements, eye examination/eye test, scan of eye, and blood tests
- Complete questionnaires
- Urine pregnancy test for women of child bearing potential
- Randomisation to NAM OR 'dummy' (placebo)
- 6-month supply of trial medication provided
  1 tablet twice daily for 6 weeks, then 2 tablets twice daily till end of trial
- Medication diary provided to all participants for completion at home

At Week 6, telephone call from your Nurse/Doctor (dose increase/dose tolerance check)

Attend visit

3 months later

Visit 2 (Month 3)

Visit 3 (Month 6)

Visit 4-6 (Months 12-24)

Attend for visits 4, 5, and 6 Every 6 months

Attend visit

3 months later

Visit 7, Month 27 (Final Visit)

- Review of medication and medication diary, BP measurements, eye examination/eye test, scan of eye, and blood tests
- Complete questionnaires
- Urine pregnancy test for women of child bearing potential

At Visits 3,4,5,6:

- Review of medication and medication diary, BP measurements, eye examination/eye test, scan of eye and blood tests.
- Complete questionnaires
- Urine pregnancy test for women of child bearing potential
- Further 6-month supply of trial medication provided
- New medication diary provided for completion at home