

The impact of Pozibio and/or Cerbella supplement on the function of the gut, brain, and gut-brain axis, from a physiological and cognitive perspective, when compared with a placebo control in healthy middle-aged and older adults.

PARTICIPANT INFORMATION SHEET

Dear _____

You are being invited to participate in one of our collaborative research studies being conducted by the Well-being and Health Assessment Research Unit (WARU) and Psychology Department at Aberystwyth University, funded by Innovate UK. Before you decide to participate, please read the information below about the project, and what will be involved. Take the time to read this information carefully and if you wish, discuss it with friends, relatives, or your GP. Please ask us if you are unclear on any information and take time to decide whether you want to take part. It is your decision.

Why have I been offered entry into this study?

You have been offered entry into this study as you have expressed interest in the activities at WARU and may be interested in participating in one of our studies. Additionally, we believe you may fit the eligibility criteria we are looking for. Taking part in this research is entirely voluntary. If you do not want to take part, please say so. If you decide to take part, you will be given this information sheet to keep (and be asked to sign a consent form). If you decide to take part, you can change your mind at any time and withdraw from the study up to one month after participation, without giving a reason. After this, the research will have been prepared for analysis and write-up, but every effort will be made to withdraw your data after this point where possible. To withdraw from the study please email waru@aber.ac.uk. You do not need to provide a reason for withdrawing.

Why is this study being performed?

Omega 3 (Ω -3) polyunsaturated fatty acids, such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), have been shown to improve learning and memory age related cognitive decline in adults. Additionally, ginseng extracts have been shown to improve cognitive performance in healthy volunteers, as well as subjects suffering from vascular dementia and Alzheimer's disease. Numerous studies suggest green tea may confer health benefits due to its pharmacological and biochemical properties. Cerbella™ soft gels contains liquid combination of fish oil (standardised to EPA and DHA), panax ginseng extract (standardised to ginsenosides), green tea extract (standardised to green tea catechins) in a flavoured base of lecithin phospholipids.

In addition, heat-treated (pasteurised or killed) probiotics (widely available in foods and drinks, such as yoghurt or kombucha) known as *postbiotics* (in the form of supplements, cell-free supernatants, and purified key components), can confer beneficial immune effects, protection against bacterial infections, and maintenance of gut health which can positively impact on mental health and cognitive ability. *Postbiotics* have an advantage for food industry applications as they can easily be supplemented in several food lines/products and are shelf stable. PoZibio™ capsules contain the probiotics *Lactobacillus paracasei*, which is a species of lactic acid bacteria (often used in the fermentation of dairy products) which has been heat-killed in PoZibio™. It's found in the human intestinal tract and mouth, but also in foods such as yogurt and naturally fermented vegetables and milk.

We would like to explore if consumption of Cerbella™ soft gels or PoZibio™ capsules, in healthy middle aged and older subjects (>60 years), is beneficial in terms of cognitive function and overall health and well-being when compared to a placebo control.

What exactly would I have to do as a participant?

First you will have to complete an eligibility questionnaire within REDCap (you will receive the link from the WARU email address upon indicating your interest to participate). The eligibility criteria are as follows:

- Participants need to be aged 60 years or older
- Participants must be able to provide written informed consent PRIOR to performing any study procedures.
- Participants must be able to commit to visits to WARU (Aberystwyth based) or Trimsaran (South Wales based) Community Centre
- Participants must be willing to complete a series of questionnaires including the: Pittsburgh Sleep Quality Index (PSQI), Mini Mental State Exam (MMSE), 36-Item Short Form Health Survey (SF-36), Warwick-Edinburgh Mental Wellbeing Scale (WEMWS), and the Gastrointestinal Symptom Rating Scale (GSRS).
- Participants must be willing to provide biofluid samples [capillary bloods, stool, and urine samples] and commit to EEG appointments.

Following completion of the eligibility questionnaire, you will be invited to an in-person induction session. This will allow us to measure your height, weight, waist, and hip circumference, and to allow us to run through the Mini Mental State Exam with you (which will take approximately 5 minutes). We will also introduce you to, and provide you with, the urine and stool home sampling kits, which you will use to collect your day 0, and day 60, samples (as instructed by the research team). This will also provide you with the opportunity to ask any questions, and for us to schedule your day 0 appointment. Two days prior to your day 0 appointment, we will send you a link via email for you to complete the following questionnaires within REDCap: the Gastrointestinal Symptom Rating Scale (GSRS), the 6-Item Short Form Health Survey (SF-36), the Warwick-Edinburgh Mental Health Well-being Scale (WEMWBS), and the Pittsburgh Sleep Quality Index (PSQI). These questionnaires will take approximately 20 minutes to complete and will allow us to obtain self-reported data for your overall health and wellbeing prior to you participating in the trial. If you do not have access to a computer (or if you do not have an email address), then we will also you to complete these during your day 0 appointment.

Prior to your day 0 appointment, you will be randomised to one of four supplements, (1 x Cerbella™ soft gels daily and 1 x placebo soft gels daily; 1 x Pozibio capsules daily and 1 x

placebo capsules daily; 1 x Cerbella™ soft gels daily and 1 x Pozibio capsules daily; 1 x placebo soft gels daily and 1 x placebo capsules daily) for 60 days, which are to be consumed in the morning. You will be provided with these supplements upon completion of your day 0 activities. Please note that the soft gels are NOT suitable for vegetarians or vegans. Randomisation will be double-blinded, so neither you nor the researcher will know what group you're in until after the end of the study.

The Workflow [for participants in Aberystwyth]

Whilst undergoing the study, if necessary, we will be easily contacted by email, Teams and phone.

Online Eligibility Session

You will be asked to provide some basic details (name, DOB, gender, preferred contact method), and to answer some medical health questions, within REDCap (compliant with GDPR standards), to help us assess your eligibility. You will be informed upon completion of the survey, whether or not you are eligible to take part. The researchers will also be notified and will be in touch shortly to arrange your in-person induction session.

In-Person Induction Session

During this session you will be asked to sign a consent form, and we will measure your height, weight, waist, and hip circumference. We will also run through the Mini Mental State Exam with you, followed by an overview of the questionnaires that you will be sent the link to complete (following this appointment), to ensure you understand what is asked of you. We will schedule your day 0 and day 60 appointments, and we will also introduce you to, and provide you with, the urine and stool home sampling kits, which you will need to use to collect your day 0 and day 60 urine and stool samples. You will collect your morning urine sample on the morning of your scheduled EEG appointment, and you will collect a stool sample within 12 hours of your day 0 and day 60 EEG appointments. Finally, you will have the opportunity to ask any questions or raise any potential concerns you may have.

BEFORE your day 0 appointment:

2 days before your first week 0 appointment, we will send you a REDCap link which will allow you to complete the following questionnaires online, which will take approximately 20/25 minutes to complete in total: the Gastrointestinal Symptom Rating Scale (GSRS), the 6-Item Short Form Health Survey (SF-36), the Warwick-Edinburgh Mental Health Well-being Scale (WEMWBS), and the Pittsburgh Sleep Quality Index (PSQI). We ask that you complete these questionnaires the day before, or the day of, your appointment. However, if you don't have access to a PC, or if you forget to complete them prior to your appointment, then we will provide you with a laptop (or paper copies of the questionnaires) so you can complete these during your first appointment (whilst we set up the EEG cap).

Day 0 Visit 1

You will be invited for a short visit to have your bloods taken. This will be a capillary sample (a prick to the finger). The visit will take no longer than 10 minutes, but will need to be in the morning as you will need to be fasted.

Day 0 visit 2 (within 48 hours of your blood sample)

Prior to your arrival, please ensure that your hair is clean, dry, and free of any product. This will help to improve the quality of your data and reduce set-up time. Please also ensure you bring your stool and urine samples with you to this appointment. Your stool sample should have been collected within the 12-hour period prior to your appointment, and the urine should be collected on the morning of your appointment. We also encourage you to go to the toilet and to eat/drink before your appointment, because once the EEG cap is in place, you will be asked to sit still for the remainder of the testing session. The EEG cap preparation time will take approximately 25-30 minutes.

Once the cap is correctly set-up, you will first be asked to complete a series of tasks within a computer program called E-Prime. The tasks are an 'eyes open/closed task' to obtain an EEG for your resting state, followed by the Stroop task and Go/No-go task, for behavioural and cognitive assessments of working memory, response inhibition and mental flexibility. You shall be provided with thorough instructions before each task, followed by a practice round with the researcher present, and you will have the opportunity to ask any questions, before each experiment begins.

After each task, the EEG program will be stopped, and a new data file will be created, before recording for the following task takes place. This will provide the opportunity in between tasks for a sip of water, or a toilet break, if necessary, although the EEG cap will have to remain in place. Altogether these tasks shall take approximately 30-40 minutes to complete. We encourage you to bring your own bottled drinks, and snacks will be available, although these will need to be consumed before or after testing. Please note that upon completion of the experiments, you will not receive any scores indicating how you have performed. However, once you have finished your full participation in this study, if you are interested in the overall general findings of the study, then please email WARU@aber.ac.uk.

Following your participation, you will have the opportunity to use the onsite showers located within the Carwyn James Building, before collecting your supplements from the WARU team.

Day 60 EEG and Behavioural Tasks

After the 60-day supplementation period, we would like you to complete the activities that you undertook during testing day 0. Once again, we will send you a REDCap link 2 days before your scheduled appointment, to complete the same questionnaires as before: the Gastrointestinal Symptom Rating Scale (GSRS), the 6-Item Short Form Health Survey (SF-36), the Warwick-Edinburgh Mental Health Well-being Scale (WEMWBS), and the Pittsburgh Sleep Quality Index (PSQI). Please remember to bring your urine and stool samples with you to your day 60 EEG appointment. We will take a capillary sample again, followed by your EEG within 48 hours. Upon your arrival for your EEG appointment, we will measure your height, weight, waist, and hip circumference, and repeat the Mini Mental State Exam. We will then fit the EEG cap and ask you to complete the same cognitive assessments that you undertook during your day 0 appointment.

After you have completed the trial, you will be sent an optional feedback questionnaire to complete.

The Workflow [for participants in Trimsaran]

Whilst undergoing the study, if necessary, we will be easily contacted by email, Teams, and phone.

Online Eligibility and Induction Session

You will be asked to provide some basic details (name, DOB, gender, preferred contact method, and home address) via phone or email, and to answer some medical health questions, to help us assess your eligibility. You will also be asked to provide rough estimations for your height and weight (so we can randomise you into one of the four arms of the trial), and the researchers will organise your first appointments. The researchers will then post your urine and stool kits with written instructions, to your home address, for you to collect your samples ready to bring to your first appointments as well as a consent form what must be posted back before sample collection. You will collect your morning urine sample on the morning of your scheduled EEG appointments at day 0 and day 60. In addition, you will collect your stool samples within 12 hours of your day 0 and day 60 EEG appointments.

BEFORE your day 0 appointment:

2 days before your first appointment, we will send you a REDCap link which will allow you to complete the following questionnaires online, which will take approximately 20/25 minutes to complete in total: the Gastrointestinal Symptom Rating Scale (GSRS), the 36-Item Short Form Health Survey (SF-36), the Warwick-Edinburgh Mental Health Well-being Scale (WEMWBS), and the Pittsburgh Sleep Quality Index (PSQI). We ask that you complete these questionnaires the day before your appointment. However, if you don't have access to a PC, or if you forget to complete them prior to your appointment, then we will provide you with a laptop (or paper copies of the questionnaires) so you can complete these during your first appointment (whilst we set up the EEG cap).

Day 0- Visit 1

You will be invited for a short visit to have your bloods taken. This will be a capillary sample (a prick to the finger). The visit will take no longer than 10 minutes, but will need to be in the morning as you will need to be fasted. During this session we will measure your height, weight, waist, and hip circumference.

Day 0- Visit 2 (within 48 hours of your blood sample)

Prior to your arrival, please ensure that your hair is clean, dry, and free of any product. This will help to improve the quality of your data and reduce set-up time. Please also ensure you bring your stool and urine samples with you to this appointment. Your stool sample should have been collected within the 12-hour period prior to your appointment, and the urine should be collected on the morning of your appointment. We also encourage you to go to the toilet

and to eat/drink before your appointment, because once the EEG cap is in place, you will be asked to sit still for the remainder of the testing session. Upon your arrival we will measure your height, weight, waist, and hip circumference, and run through the mini mental state exam with you. We will also collect your capillary blood samples. We will then set up the EEG cap (during which you can complete the above questionnaires if you do not have access to a laptop at home or if you did not have time to complete the questionnaires before your appointment). The preparation time for the cap will take approximately 25-30 minutes.

Once the cap is correctly set-up, you will first be asked to complete a series of tasks within a computer program called E-Prime. The tasks are an 'eyes open/closed task' to obtain an EEG for your resting state, followed by the Stroop task and Go/No-go task, for behavioural and cognitive assessments of working memory, response inhibition and mental flexibility. You shall be provided with thorough instructions before each task, followed by a practice round with the researcher present, and you will have the opportunity to ask any questions, before each experiment begins.

After each task, the EEG program will be stopped, and a new data file will be created, before recording for the following task takes place. This will provide the opportunity in between tasks for a sip of water, or a toilet break, if necessary, although the EEG cap will have to remain in place. Altogether these tasks shall take approximately 30-40 minutes to complete. We encourage you to bring your own bottled drinks, and snacks will be available for afterwards. Please note that upon completion of the experiments, you will not receive any scores indicating how you have performed. However, once you have finished your full participation in this study, if you are interested in the overall general findings of the study, then please email WARU@aber.ac.uk.

Following your participation, you will have the opportunity to use the onsite showers located within the Trimsaran community hall, before collecting your supplements from the WARU team.

Day 60 EEG and Behavioural Tasks

After the 60-day supplementation period, we would like you to complete the activities that you undertook during testing day 0. We will send you a REDCap link via email, 2 days before your scheduled day 60 appointment, so you can complete the same questionnaires as before: the Gastrointestinal Symptom Rating Scale (GSRS), the 6-Item Short Form Health Survey (SF-36), the Warwick-Edinburgh Mental Health Well-being Scale (WEMWBS), and the Pittsburgh Sleep Quality Index (PSQI). When you arrive for your day 60 appointment, we ask that you bring your day 60 urine and stool samples with you, and we will again run through the Mini Mental State Exam with you. We will also measure your height, weight, waist, and hip circumference, and collect your capillary blood samples.

After you have completed the trial, you will be sent an optional feedback questionnaire to complete.

For participants in Aberystwyth and Trimsaran

What will I gain?

You will receive a £20 Amazon voucher for each batch of testing sessions (day 0 and day 60), equating a total of £40 for completion of the trial which you will be provided via email. You will also allow us to gain important insight into the CerbellaTM and PozibioTM supplements, and the extent to which they support or improve overall physical and mental health in older, healthy populations, which may be applied to other cohorts such as those suffers suffering from vascular dementia and Alzheimer's disease.

Are there potential side effects?

The supplements have already been tested for any adverse effects in a human cohort, however if any negative effects occur, please refrain from continuing in the study. The supplements are NOT suitable for vegetarians or vegans.

EEG is non-invasive, however, placing the EEG electrodes along the scalp can be time consuming (approximately 30 minutes), and you will be required to sit relatively still during the application and testing process (the application and testing process combined will take approximately 1-1.5 hours). The application of the EEG cap will require EEG gel (saline solution) to be applied to your scalp, which will make your hair messy upon removal of the cap. Towels will be placed along your shoulders to avoid the solution meeting your clothes, and these towels (in addition to paper towels) will be provided to remove any excess gel from your hair. Hair washing facilities will also be available in the [Aberystwyth cohort: Carwyn James Building; Trimsaran cohort: Trimsaran Community Hall] for you to use. In addition, capillary blood draws can cause localised soreness to your fingers.

What if I no longer want to be a part of the study?

Whilst we would be sorry to see you leave the study, participation is entirely voluntary, and you are free to withdraw at any stage without explanation. All data collected over the investigation can be withdrawn, however only up to one month after your participation. However, if you request to withdraw your data at a later date, we will endeavour to withdraw your data where possible. If you chose to leave the study, this will not affect your involvement in future research studies managed by the WARU.

What if I feel unwell during the study, or if something else goes wrong during the study?

If you, or a member of your family/household become unwell during the study, please alert a member of the research team immediately using the contact information at the end of this document. Participation in the study should be suspended immediately until further discussion with the research team has taken place. If you become unwell at any point and need medical assistance, please contact 111 and seek advice from the NHS health sector or your doctor's surgery. We have a duty of care towards you and can help monitor your health remotely over 14 days and will help in any way we can.

Will the information and data be confidential?

Yes. Only those researchers involved will be able to look at the information you provide. Specific details, which identify you, will only be available to the researchers, and they will be stored in a password-protected file on OneDrive. Any paper files containing identifiable information (i.e. your consent form) will be stored in a lockable cabinet in a key-card secured office that only the immediate research team have access to. After the end of the study, any information relating to you will be made pseudonymous (coded without your name associated). You will not be identifiable in any publication that may arise from this research. If you meet the exclusion criteria for the study, then your personal details shall be removed from the study.

Please note that in exceptional circumstances confidentiality may have to be breached in cases where persons are considered to be at risk or if required by law.

Will my GP be informed?

No.

What will happen to the samples collected?

Any paper questionnaire data will be made into a digital copy in REDCap , associated with your unique, pseudonymised code, and the paper versions will be stored in a locked filing cabinet. Your blood, stool, and urine samples will be examined at analytical laboratories in Aberystwyth University, AberInnovation and Bronglais Hospital (biochemistry). All samples will be stored securely and anonymously. Upon completion of the study, the samples will be destroyed or stored in our laboratory freezers in accordance with government regulations. Your name and details will no longer be associated with the samples. Samples will be securely stored for future use if further validation is required, for up to 5 years.

Who has reviewed the project?

This project has been reviewed and approved by the Research Ethics Panel, Aberystwyth University (ethics@aber.ac.uk). In accordance with the British Psychological Society's Code of Ethics and Conduct, as the research team, we are required to conduct the research in accordance guidelines set out.

Does the project conform to GDPR guidelines?

This research is being conducted in accordance with the GDPR guidelines. The AU Data Protection Manager provides oversight of AU activities involving the processing of UK GDPR and special category data, and can be contacted at infocompliance@aber.ac.uk. Your personal data will be stored securely and processed for metabolomic analysis. The legal basis that would be used to process your personal data will be 'a task in the public interest'. If you are concerned about how your personal data is being processed, please contact AU in the first instance at infocompliance@aber.ac.uk. If you remain dissatisfied, you may wish to contact the Information Commissioner's Office (ICO). Contact details, and details of data subject rights,

are available on the ICO website at: <https://ico.org.uk/for-organisations/data-protection-reform/overview-of-the-gdpr/individuals-rights/>.

What do I do next?

Either contact the WARU team (waru@aber.ac.uk) or phone 07974 883662 to confirm you wish to proceed, and we will contact you shortly. If you have any further questions after reading this document, please do not hesitate to contact us. We hope you agree to participate and look forward to hearing from you very soon.

Many thanks,
The WARU Team

Contact for support:

Samaritans: 01970 116 123

jo@samaritans.org

<https://www.samaritans.org/branches/samaritans-aberystwyth-and-mid-wales>

Mind: 01970 626 225

info@mindaberystwyth.org

<http://mindaberystwyth.org/>

Mentalhealth.org.uk: <https://www.mentalhealth.org.uk/your-mental-health/getting-help>