# Research Study Protocol

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| **Full Title:** | **Ageing Gut-Brain Interactions** |
| Study Acronym: | AGEING-GB |
| Sponsor: | University of Aberdeen |
| Sponsor Reference Number: | 2/103/17 |
| Funder: | Tenovus Scotland & NHS Grampian |
| Chief Investigator: | Professor Phyo Myint |
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| Version Number and Date: | Version 3.0; 28 February 2018 |
| Co-Investigators: | Prof Alex Johnstone<br>Dr Alison Donaldson<br>Dr Karen Scott<br>Dr Emma Law<br>Dr Roy L Soiza |

**Protocol Approval**

**Ageing Gut-Brain Interactions Signatures**

By signing this document I am confirming that I have read, understood and approve the protocol for the above study.

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|---|---|---|
| PHYO MYINT |  | 28 February 2018 |
| Chief Investigator<br>**Professor Phyo Myint** | Signature | Date |

**List of Abbreviations**

| | |
|---|---|
| AD | Alzheimer's Disease |
| CRF | Case Report Form |
| CNORIS | Clinical Negligence and Other Risks Scheme |
| GCP | Good Clinical Practice |
| ISF | Investigator Site File |
| SCFA | Short Chain Fatty Acid |
| SMG | Study Management Group |
| SOP | Standard Operating Procedure |
| TMF/SMF | Trial/Study Master File |

**Summary**

This research project will address a desperate need for evidence on how diet could be used to treat and improve symptoms of Alzheimer's disease (AD). It has been estimated that 36 million people have dementia worldwide, and in older people Alzheimer's disease accounts for 60–70% of all dementia. Research supports the hypothesis that modifiable lifestyle-related factors are associated with cognitive decline, which opens new avenues for prevention or modification of disease.

The concept that inspires this proposal 'Ageing-Gut-Brain Interactions study' is that our gut microbiota impact upon the gut-brain axis and thereby on behaviour, including challenging behaviours often associated with dementia. In the absence of available cures for Alzheimer's disease, diet is an important modifiable component but we currently have little knowledge about the role of diet in clinical symptoms of dementia. A recent study from Ireland from the European Union funded Nu-Age cohort reported that the gut microbiota profile in the elderly was different between community-living and institutionalized individuals, with specific microbiome profiles correlating with frailty and poor health.

Changes in dietary composition and diversity were considered the main drivers of the shifts in gut bacteria profile. In this multi-disciplinary research study, we will investigate the gut microbiota composition in people with Alzheimer's dementia with challenging behaviours, test the feasibility of recruitment, and provide initial data to support a future grant application involving a dietary intervention study in patients with Alzheimer's disease.

We will test our hypothesis that the gut-brain axis promotes behavioural changes in Alzheimer's dementia and is responsive to changes in gut microbiota profile, by comparing the gut microbiota profile between three participant groups (1) Alzheimer's dementia with challenging behaviour, (2) Alzheimer's dementia without challenging behaviour, and (3) a control group of healthy age-matched elderly. We will also carry out a survey to care homes to assess their willingness to participate in dietary supplementation study.

# 1. Introduction

## 1.1. Background

Healthy life expectancy is a key area of research. It has been estimated that 36 million people have dementia worldwide (Prince et al., 2013) and that there are 4.6 million new cases of dementia every year (Ferri et al., 2005). Epidemiological evidence supports the hypothesis that modifiable lifestyle-related factors are associated with cognitive decline, opening new avenues for prevention (Solfrizzi et al., 2008). Alzheimer's disease is the commonest cause of dementia in older people, accounting for 60–70% of all dementia cases when using traditional diagnostic criteria for dementia subtypes (Blennow et al., 2006; Fratiglioni et al., 1999).

There are no available cures for AD, but an alternative approach is to use strategies that delay disease progression at an early stage (Lobo et al, 2000). Optimal brain function results from highly complex interactions between numerous genetic and environmental factors, including food intake, physical activity, age and stress (Solfrizzi et al, 2008). Diet in particular has become the object of intense research in relation to cognitive aging and neurodegenerative diseases.

The gut microbiota is a large, diverse collection of microbes, collectively containing 100 times more genes than the host. It is host-specific, contains heritable components, can be modified by diet, surgery or antibiotics, and in its absence nearly all aspects of host physiology are affected (Marchesi et al, 2016). We now realise that the human microbiota is a previously overlooked system that makes a significant contribution to human biology and development.There is a new and exciting field of research with limited published data in the elderly (Mariat et al, 2009; Claesson et al, 2012), that could provide a basis for the design of novel, microbiota-targeted, therapies to improve care of older people who suffer from Alzheimer’s dementia.

There is increasing evidence that identifies the gut microbiota as a key conduit between nutrition and brain function (Goyal et al., 2015). Reduction in the frequency of genes encoding short chain fatty acid (SCFA) production was prominent among institutionalized older adults, as were increases in circulating pro-inflammatory cytokines tumour necrosis factor-alpha, interleukins-6 and -8, and C-reactive protein (Claesson et al., 2012).

### 1.1. Rationale for Study

***Hypothesis: The composition and/or diversity of the gut microbiota is different between healthy elderly and those with Alzheimer's dementia, who do or do not exhibit behaviour(s) that are challenging***

The concept that inspires Ageing-GB is that our gut microbiota impact upon the gut-brain axis and thereby on behaviour. We need to understand the nature of that impact, the underlying mechanisms, and how changes in diet can reprogram our gut microbiota-brain axis to resolve or reduce clinical symptoms associated with Alzheimer's dementia.

However, there has been no published work that we are aware of to examine the gut microbiota profile in patients with Alzheimer's disease. Consequently, first we need to demonstrate the differences in microbiota profile between AD patients with or without behaviours that are more challenging to manage. We believe that our work will be fundamental to provide evidence to support dietary modification or supplementation as cost-effective and safe avenues for alleviating signs and symptoms of dementia in this vulnerable group and thus reduce the carer burden.

This study will require the co-operation of care home managers and staff, and will thus simultaneously assess the feasibility of performing a nutritional intervention study in this group of individuals, in this setting.

## 2. Study Objectives and Outcomes

### 2.1. Objectives

#### 2.1.1. Primary Objective

To compare the composition and activity of the gut microbiota in three groups of elderly individuals: (i) Alzheimer's dementia and challenging behavioural symptoms, (ii) Alzheimer's dementia and no challenging behavioural symptoms, (iii) and people without dementia of any type.

#### 2.1.2. Secondary Objective

To assess the willingness of care homes and carers to participate in a research trial investigating the links between diet and Alzheimer's dementia.

### 2.2. Outcomes

#### 2.2.1. Primary Outcome

Differences in the composition and activity of gut microbiota between three groups.

#### 2.2.2. Secondary Outcome

The feasibility of undertaking a study with this group of elderly, vulnerable people in a care home setting including assessing the feasibility of the outcome of the future trial such as quality of life outcome.

## 3. Study Design

### 3.1. Study Description

An observational case-controlled study with three groups of participants with 1:1:1 will be carried out. A total of 60 volunteers, 20 in each group from the following groups (i) Alzheimer's dementia and challenging behavioural symptoms, (ii) Alzheimer's dementia and no challenging behavioural symptoms, (iii) without any type of dementia, will be recruited from care homes.

Each volunteer (assisted by staff) will provide two faecal samples, at least a week apart which will be analysed for microbial composition and activity by assessing Short Chain Fatty Acid profile (SCFA profile). Faecal samples will be collected using a pot on a toilet/commode, which will be sealed and processed in the laboratory within 12hr.

Additional information on regular diet composition will be collected by accessing the weekly care home menu. Staff will observe participants and record every episode which requires staff intervention as a result of behaviours that are challenging to manage.

A quality of life questionnaire will be completed by each volunteer in Alzheimer's dementia groups using DEMQOL (Dementia Quality of Life questionnaire).

DEMQOL is widely used patient reported outcome measures (PROMs) of health related quality of life in people with dementia.

Finally, we will collect other information on medication, personal characteristics, co-morbidities etc. to mitigate any confounding effects.

To achieve the secondary objectives the following outcomes will be assessed.

We will collect information on the following key aspects of feasibility of a larger study (future clinical trial) based on the main hypothesis driven work carried out under aim 3 described below

(1) Proportion of eligible older people with Alzheimer's dementia with or without challenging behaviours

(2) Proportion of eligible participants willing to participate

(3) Proportion of participants who are able provide samples in each group

(4) Proportion of participants (staff who are looking after them or relatives) who are able to provide study data /information

We will assess participants, their carers and whenever relevant managers and staff of care home and relatives/family members and people with Alzheimer's dementia with regard to willingness to participate in a research trial and to identify issues to be addressed to gain support for such an intervention trial through end of study questionnaire conducted by the study research nurse face to face.

This will explore the practical issues which need to be considered in the future study. A study completion questionnaire will be introduced after sampling is complete (Appendix B).

### 3.2. Study Matrix

| Components | Objectives | Tasks |
|---|---|---|
| Case-control study | Primary + Secondary | See study matrix below |
| Completion questionnaire | Secondary | See study matrix<br>Appendix B |
| Care home survey | Secondary | Appendix A |

Study Matrix for case-control study

| Measurements | At enrolment (after consent) | Week 1 | Week 2 |
|---|---|---|---|
| Demographics | X | | |
| Height | X | | |
| Weight | X | | |
| Co-morbidities | X | | |
| Medications | X | | |
| Mini Nutritional Assessment | X | | |
| Food Menu | X | | |
| Faecal Samples | | X | X |
| Behavioural chart | X | | |
| DEMQOL in AD groups | X | | |
| Completion exit questionnaire | | | X |

## 4. Study Population

### 4.1. Number of Participants

(i) with Alzheimer's dementia and challenging behavioural symptoms (n=20)
(ii) with Alzheimer's dementia and no challenging behavioural symptoms (n=20)
(iii) with no dementia (n=20)

### 4.2. Inclusion Criteria

Resident in a care home

### 4.3. Exclusion Criteria

1. Use of antibiotics in the last 8 weeks
2. Active gastrointestinal disease.
3. Unable to provide informed consent

## 5. Participant Selection and Enrolment

### 5.1. Identifying Participants

Research nurse will perform the initial approach to local care homes to determine whether they are willing to be involved in the study. This will be done first by contacting care homes by telephone and follow up visit or post to the care home with the study information package. At this point the care home manager will be asked to identify individuals within each care home who may fall into one of the three study groups. These individuals (or their carer, legal guardian or person with power of attorney) will be approached to see if they are interested in participating in the study. If they were interested to speak to research team, then the research nurse will explain about the study and give study information for them to consider the study participation.

### 5.2. Consenting Participants

Consent will be taken by the study research nurse who has appropriate training. Consent will be recorded appropriately on the study consent form.

For end of study questionnaire, participants' consent will be taken specifically.

### 5.3. Screening for Eligibility

In order to be recruited into study group (i) or (ii) there has to be an existing medical diagnosis of Alzheimer's dementia that will be confirmed by cross-referencing with medical records. Likewise for recruitment to group (iii) no such diagnosis should exist. The sub-group stratification of Alzheimer's dementia patients with or without behaviours that are challenging will be ascribed after speaking to care home staff and analysing care home records of participants.

Eligibility will be determined based on the knowledge of care home manager and staff. At this stage, the research team will not have any knowledge of who they are. Potentially eligible participants will first be approached by care home manager/staff to enquire whether they would be willing to speak to research team. Only those who are willing to speak to research team will be approached by the research nurse and provide study information. If they are interested and provide permission to check the eligibility, the diagnosis will be checked against their care home records. In case if the care home staff deem the potential participant lacks capacity, formal capacity assessment will be carried out by medically trained research team member.

Initial screening for eligibility will be carried out by care home staff and second level screening by study team will only happen after the participant has provided informed verbal consent prior to participation. If eligible written informed consent will be taken for study procedures.

### 5.4. Ineligible and Non-Recruited Participants

Only eligible volunteers will be recruited to the study, up to the required number in each group. Once this number is reached, any additional interested volunteers will be thanked for their interest. No data will be collected prior to recruitment.

## 6. Withdrawal Procedures

If any participant wishes to withdraw from the study at any point after recruitment, all data and samples collected will be destroyed. If the carer perceives that participation in the study is causing distress to the volunteer, they will provide advice but if the distress persists the volunteer may be withdrawn from the study. In both cases a 'withdrawn from study' form will be completed and attached to the CRF. Unless such a form is completed (by either the volunteer or their representative) and consent is thus withdrawn, all samples will be kept following appropriate study guidelines. As the study requires 20 participant in each arm of the study, we will replace the withdrawal with further recruitment.

## 7. Data Collection and Management

### 7.1. Data Collection

Faecal samples will be analysed for SCFA profile and DNA bacterial profile. Samples will be stored with anonymised labels for up to 10 years. The volunteer phenotype (informing the study group) will be recorded on the CRF. Consent will be sought from subjects to collect faecal samples. Samples from Aberdeen nursing homes will be collected to maintain/ensure sample quality and integrity. These will be collected from the care home by one of the research staff from the Rowett Institute. All food diaries and other questionnaires will be anonymised following recruitment, and stored in a locked filing cabinet in the care home manager's office prior to collection by study researchers. Final storage will be locked filing cabinets in Human Nutrition Unit, or on a secure shared drive, accessible only by the researchers and auditors of the sponsor (for auditing purpose).

### 7.2. Data Management System

All data subsequently collected will be stored appropriately. Participants' identities are strictly confidential. We will allocate a unique subject code for the individual participants and all the data will be recorded using this code. Only the research team will have access to participants' full details, which will be saved on a shared drive with limited access on password-locked University computers. The hard copy will be stored in locked filing cabinet.

The CI will authorise and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject. Data collection will be the responsibility of the CI in this study. Data will be recorded on paper CRFs, which will subsequently be entered onto a secure, password protected study database in SPSS format, by the research team. Electronic database will be held within University computer system in a shared study folder with restricted assessed to study team members and statisticians involved in the study who will be identified in study delegation log. All CRFs and original paper data will be safely stored in locked filing cabinet and researchers will be able to double check the raw data with the electronic file and original file. Database is owned by researchers and the Chief Investigator is the data controller. Data will be entered twice for validation purpose. Data queries will be addressed by the research team members with specific statistical expertise. All University data were stored with a back-up. CRF data will be part of the database. Database may hold additional data collected from the questionnaire surveys; these will be in the form of separate sheets of data which will form complete database.

Subjects will not be identified by name in the study database or on any study documents to be collected, but will be identified by a unique subject number. Source data are contained in source documents (original records). All the source data will be recorded in CRFs or original document form from research team. Data will be transferred into an electronic file and saved in password lock computer. All data will be transferred into an SPSS/Excel files as appropriate by the research nurse. A copy of the CRF will remain at the Investigator's site file at the completion of the study.

Some of the samples will be sent, anonymously, to the bioinformatics team at the University of Aberdeen for final analysis. This means samples will be referred to by the unique study ID number. Any information collected by these third parties will utilise these coded details for all data output. Support provided by Statisticians from biomathematics and Statistics Scotland.

## 8. Labs and Samples Analysis

Level 5 laboratory at The Rowett Institute, University of Aberdeen will be where the faecal sample analysis will be conducted, under supervision of Dr Karen Scott. The samples will be analysed for short chain fatty acid profile (SCFA) and the bacterial DNA will be extracted for genome analysis. When the study is complete, the faecal samples will be destroyed.

**8.1.** The faecal/stool samples will be collected by inserting the sample collection container (pre-lined with two plastic bags, the inner one with holes) into the commode when the volunteer needs to defecate. The carer will separate the bags and store the sealed bag containing the faecal sample only in the sealed container and inform the lab that a sample is ready for collection. Samples will be transferred to the Rowett institute (University of Aberdeen) and stored in a -70 +/-5 $^{O}$C freezer in a glycerol buffer for up to 2 weeks prior to DNA extraction. Extracted DNA will be further stored in a -70 +/-5 $^{O}$C freezer in the Cat 2 grade lab until all volunteers finish the trial. All the samples will be anonymised. All freezers are calibrated and monitored by research team regularly. Final analysis (by the Bioinformatics team) will be done at the end of the study.

After carrying out necessary tests, the samples will be destroyed as per sponsor's regulations of disposing samples.

## 9. Statistics and Data Analysis

### 9.1. Sample Size Calculation

We have examined existing data held at RINH with the statisticians from Biomathematics and Statistics Scotland (BioSS) on gut bacteria in faecal samples. The power calculations indicate that with 20 volunteers on a controlled diet the sample will provide at least 90% power to detect shifts of 20% or more in SCFA and metabolites, and a difference of 45% or more in bacteria between groups. Previous studies have shown that such shifts are achievable in healthy and diseased patient groups.

### 9.2. Proposed Analysis

Data will be analysed using SPSS (latest version available at the time of analysis). Data will be presented descriptively and comparisons will be made among 3 groups. Parametric and non-parametric statistical tests will be applied for normally and non-normally distributed data, respectively.

Care home survey data will be analysed using descriptive analysis to estimate the secondary objectives. Textual data will be transcribed verbatim and themes will be derived using thematic analysis.

Questionnaire data will also be transcribed verbatim and summarised based on emerging theme bases on experiences and views of participants (when able to provide consent), carers and family members.

### 9.3. Missing Data

The two time points in this study will be used to show consistency of microbial profiles within an individual. If there are missing data points then a reduced dataset of the double time points will be analysed, and an additional analysis of single time points will be made. Having double collection times from each individual will also test the feasibility of the collection process for the main study. We will collect menus from both weeks preceding sample collection in order to have some dietary record in the immediate run-up to sample collection.

### 9.4. Transfer of Data

All researchers on the study will have access to University of Aberdeen shared computing facilities where the data will be stored so there will be no data transfer between sites. Samples transferred from care homes to the laboratory will be in anonymised containers labelled with volunteer number. Hard copies of questionnaire data will be transferred directly from the care home to the office and not left in vehicles overnight. For research team members who are not staff members of UoA will either have access through honorary contract or via data transfer agreement between UoA and their respective Institutions.

The data will be used to apply for further grant application for subsequent study and for the publication purpose. The data will be stored for six years after the last publication as per the local guidance and for the purpose of audit.

## 10. Trial/Study Management and Oversight Arrangements

### 10.1. Trial/Study Management Group

The study will be co-ordinated by a Study Management Group (SMG), consisting of e.g. the grant holder (CI), co-PIs Prof Alex Johnstone, Dr Karen Scott and Dr Alison Donaldson and the Research Nurse (TBA).

This group will have overall responsibility for conduct and running of the study.

### 10.2. Trial/Study Management

A Research Nurse will oversee the study and will be accountable to the CI. The Research Nurse will be responsible for checking the CRFs for completeness, plausibility and consistency. However, this remains the overall responsibility of the CI. Any queries will be resolved by the CI or delegated member of the study team.

A study-specific Delegation Log will be prepared and will be kept in the Trial Management Site file. The delegation log will have information of detailed the responsibilities of each member of staff working on the study. This site-specific delegation log will be held by the care home manager and will only contain details of the individuals recruited to the study within that care home. The overall study master file will be held by the CI and this file will contain full details and CRFs of all the volunteers recruited.

### 10.3. Trial/Study Steering Committee

The SMG will oversee the conduct and progress of the study.

### 10.4. Data Monitoring Committee

The SMG will oversee study progress. It is not thought necessary to have separate groups for this with the relatively small study involved here.

## 11. Inspection of Records

**12.1**

The CI shall permit study related monitoring, audits, and REC review. The CI agrees to allow the Sponsor or, representatives of the Sponsor, direct access to all study records and source documentation.

## 12. Good Clinical Practice

### 12.1. Ethical Conduct of the Study

The study will be conducted in accordance with the principles of good clinical practice (GCP).

In addition to Sponsorship approval, a favorable ethical opinion will be obtained from the appropriate REC and appropriate NHS R&D approval(s) will be obtained prior to commencement of the study.

### 12.1.1. Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access to study staff only. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor or its designee. The CI and study staff involved with this study will not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee will be obtained for the disclosure of any said confidential information to other parties.

### 12.1.2. Data Protection

The CI and study staff involved with this study will comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. The CI and study staff will also adhere, if appropriate, to the current version of the NHS Scotland Code of Practice on Protecting Patient Confidentiality. Access to collated participant data will be restricted to the CI and appropriate study staff.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

### 12.1.3. Insurance and Indemnity

The University of Aberdeen is Sponsoring the study.

**Insurance** –

- The University of Aberdeen will obtain and hold a policy of Public Liability Insurance for legal liabilities arising from the study.

- Where the study involves University of Aberdeen staff undertaking clinical research on NHS patients, such staff will hold honorary contracts with Grampian Health Board which means they will have cover under Grampian's membership of the CNORIS scheme.

**Indemnity:** The University of Aberdeen does not provide study participants with indemnity in relation to participation in the Study but have insurance for legal liability as described above.

## 13. Study Conduct Responsibilities

### 13.1. Protocol Amendments, Deviations and Breaches

The CI will seek approval for any amendments to the Protocol or other study documents from the Sponsor, REC and the relevant NHS R&D Office. Amendments to the protocol or other study docs will not be implemented without these approvals.

In the event that a CI needs to deviate from the protocol, the nature of and reasons for the deviation will be recorded in the CRF, documented and submitted to the Sponsor. If this necessitates a subsequent protocol amendment, this will be submitted to the Sponsor for approval and then to the appropriate REC and lead NHS R&D Office for review and approval.

In the event that a serious breach of GCP is suspected, this will be reported to the Sponsor immediately using the form "Breach Report Form".

### 13.2. Study Record Retention

Archiving of relevant study documents will be authorized by the sponsor at the end of the study. Essential documents will be archived for a minimum of 6 years after completion of the study. Documents which are not to be archived will be destroyed (with authorization from the sponsor). Study documents will be archived in line with the sponsor SOP in the Health Sciences Building archive. UoA. Prior to archiving, during the study, material will be stored in locked filing cabinets, located in archive room in Human Nutrition Unit at the Rowett Institute.

### 13.3. End of Study

The end of study is defined as collection and processing of the last sample from the last volunteer. The Sponsor, CI and/or the TMG have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the Sponsor and REC within 90 days, or 15 days if the study is terminated prematurely. The CI will ensure that any appropriate follow up is arranged for all participants.

A summary report of the study will be provided to the Sponsor and REC within 1 year of the end of the study. A summary brief will also be provided to all participating care homes.

## 14. Reporting, Publication and Notification of Results

### 14.1. Authorship Policy

Ownership of the data arising from this study resides with the study team and their respective employers. On completion of the study, the study data will be analyzed and tabulated, and a clinical study report will be prepared.

### 14.2. Publication

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinical areas (where appropriate and according to their discretion).

### 14.3. Peer Review

This project has received funding from Tenovus Scotland and the NHSG Endowment fund, and has thus been peer reviewed by both funders. It has also been reviewed by the Rowett Human studies management group prior to submission to funders.

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