

# ENVISION PROTOCOL

## Aspirin for the prevention of cognitive decline in the Elderly: a Neuro-Vascular Imaging Study (ENVIS-ion) of ASPREE

### **Sponsor Institution**

Monash University

### **Chief Investigators**

A/Pr Marc Budge

Prof Elsdon Storey

Prof Andrew Tonkin

Prof Tien Wong

A/Pr Christopher Reid

Prof David Ames

### **Associate Investigators**

Dr Andrew Janke

Dr Robyn Woods

A/Pr Jie Jin Wang

Dr Rohan Essex

Prof John McNeil

Prof Marjan Kljkovic

### **Contact details:**

Dr Robyn Woods

Department of Epidemiology & Preventive Medicine

Monash University

Alfred Hospital, 3rd Floor Burnet Building

89 Commercial Road, Melbourne VIC 3004

Phone – (03) 9903 0345 Fax – (03) 9903 0556

**PROTOCOL SIGNATURE PAGE**

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**Principal Investigator: Professor Elsdon Story**

*Signature*

*Date* **26 March 2008**

This document is confidential. The Investigator declares that they have read the final study protocol. The Investigators will conduct the study according to the procedures specified in the study protocol, in accordance with ICH GCP (annotated with TGA comments) and according to the principles of the National Statement on Ethical Conduct in Human Research, 2007 published by the National Health & Medical Research Council

*Name of Study Investigator* \_\_\_\_\_

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*Signature of Study Investigator*

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*Date*

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## **1. BACKGROUND**

Adults over 70 years of age represent the fastest growing segment of the population. Consequently, “successful” cognitive ageing has become a significant goal for preventative medicine.

Australia already has an “epidemic of dementia”, which is projected to become the leading cause of disability by 2016.<sup>1</sup> Brain white matter ischaemia may cause cognitive decline in its own right, but is also present in the majority of those with Alzheimer’s disease (AD). Vascular risk factors have emerged as important contributors to the development of AD and sub-clinical brain infarcts / ischaemia - the combination of which is the most common pathology found in community-based studies of older adults with cognitive decline.<sup>2-3</sup> Therefore, small-vessel, vascular disease is an attractive target for primary preventative therapy.

Brain magnetic resonance imaging (MRI) changes correlate with white matter ischaemia / infarction, and potentially provide an efficient surrogate for cognitive decline. However, MRI is relatively costly and is not universally accessible, making it impractical for population screening. The retinal vasculature shares many features with that of the brain. So, should changes in the two be highly correlated, retinal digital photography would provide the opportunity to combine a relatively inexpensive, widely available tool with automated analysis to select those likely to benefit most from a preventative intervention like regular low-dose aspirin treatment.

The ENVIS-ion study aims to examine whether regular low-dose aspirin reduces the rate of increase of brain MRI-based White Matter Hyperintensity (WMH) and Silent Brain Infarction (SBI) volumes in healthy elderly Australians of both genders. The randomised, double-blind, placebo-controlled trial will be carried out over 5 years in 600 people who are over 70 years of age and who are cognitively normal (for age) and generally in good health in a general practice setting.

Findings from this study will complement the parent study (ASPREE) which has as its primary question whether regular aspirin prolongs life free of mental and physical disability. Death from all causes, cardiovascular morbidity, dementia, cognitive decline and physical impairment will be measured over 5 years follow-up in 18,000 cognitively normal (for age) healthy, older ( $\geq 70$  years old) adults in a general practice setting.

## **2. PRIMARY AIMS**

- To examine, in a 5-year randomised, double-blind, placebo-controlled trial of cognitively normal (for age) healthy, older adults in a general practice setting, whether

regular low-dose aspirin reduces the rate of increase of brain MRI-based WMH and SBI volumes;

- To determine whether changes in retinal vascular imaging parameters, including quantitatively measured retinal arteriolar and venular calibre and the presence of retinal arteriolar pathology, parallel brain MRI changes over 3 years;
- To examine whether regular low-dose aspirin will reduce the extent of changes in these retinal vascular parameters;
- To establish whether the level of baseline cognitive function in 'cognitively-normal' older adults, including both global and executive domain-specific measures, correlates with baseline MRI- WMH and SBI volumes and retinal vascular parameters;
- To establish whether MRI-based WMH and SBI volumes and retinal vascular parameter changes over 3 years correlate with cognitive decline over this period;
- To examine whether the effect of aspirin on MRI-based WMH and SBI volumes, if found, is modified by readily-available clinical parameters (age, gender and hypertensive status).

### **3. METHODS**

*(methods for the ASPREE 'parent' study are described in detail in the ASPREE protocol)*

#### **3.1 ENVIS-ion Study Design**

As with the ASPREE study, ENVIS-ion is a randomised, double-blind, placebo-controlled trial of 100 mg enteric-coated aspirin versus placebo. Randomisation will be stratified for general practice and for age (70-79 or  $\geq 80$  years).

All ASPREE participants who have no known contraindications to MRI are deemed eligible for entry into the ENVIS-ion sub-study. At the screening visit for the commencement of the placebo label run-in phase, subjects will be approached for participation in the ENVIS-ion sub-study. Written informed consent will be obtained from those subjects who are willing to enter the sub-study. They will be provided with an appointment for further cognitive testing, baseline MRI and retinal imaging to be scheduled as near as possible to the time of randomisation. Further assessments will be performed in each subject at the time of the three year follow-up visit post-randomisation.

#### **3.2 Inclusion/exclusion criteria**

Inclusion criteria for the main ASPREE study will apply. Participants in ENVIS-ion should be consecutive participants who enter the ASPREE study at each centre to maintain balance in

treatment groups according to the block randomisation procedures for the main study. Exclusion criteria for the ASPREE study will apply with the addition of the following criteria of contraindications to MRI such as metallic body parts, pacemakers, and claustrophobia.

### **3.3 Other procedures**

Two additional cognitive tests (the Stroop and Color Trails) to those undertaken in the main ASPREE study will be administered to ENVIS-ion participants at baseline and year 3.

MRI images will be captured on CD for all subjects enrolled in the ENVIS-ion study and will be sent to the core analysis laboratory (located at Dementia Collaborative Research Centre Brain Imaging Laboratory in Canberra) for analysis.

Retinal photographic images will be captured on CD for all subjects enrolled in the ENVIS-ion study and will be sent to the core analysis laboratory (located at RetVIC, The University of Melbourne) for analysis.

## **4. STUDY MEDICATION AND SUPPLIES**

*(additional details are provided in the ASPREE protocol)*

### **4.1 Run-in placebo**

A first container with placebo medication for 4 weeks will be given to participants at the screening visit. If for whatever reason a participant cannot attend their randomisation visit at 4 weeks they will receive another screening visit and supply of placebo.

### **4.2 Randomisation visit**

Subsequent to the randomisation visit each participant will be provided with a 12 months supply of study drug: either aspirin or placebo. At each annual visit each participant will be provided with the next 12 months supply of their allocated drug.

## 5. SCHEDULED VISITS AND MEASUREMENTS

*(the ASPREE scheduled visits and measurements are described in detail in the ASPREE protocol)*

Table 1 shows the measurements that will be undertaken in all ASPREE participants (first 12 rows). ENVIS-ion participants will have brain and retinal images (as outlined in 5.1 and 5.2) and two additional cognitive function tests, as outlined in 5.3, at baseline and 3 years (rows 13 and 14 of Table 1).

Measurement / Activity	Lifestyle profile & screening (Visit 1)	Assessments & eligibility (Visit 2)	Follow-up (1 yr)	Follow-up (2yr)	Follow-up (3yr)	Follow-up (4yr)	Follow-up (5yr)
1. Review inclusion/ exclusion criteria	X	X					
2. Obtain informed consent	X						
3. Dispense medication	X (placebo only)	X	X	X	X	X	
4. Assess medication compliance	X		X	X	X	X	X
5. Blood pressure, height, weight & abdominal circumference	X	X	X	X	X	X	X
6. Demographics, family & personal history & lifestyle factors	X		X	X	X	X	X
7. Laboratory testing - Fasting blood total cholesterol, HDL, LDL, glucose, creatinine & haemoglobin	X		X	X	X	X	X
8. Quality of life - SF-12	X		X	X	X	X	X
9. Assess cognitive function - 3MS <sup>a</sup> , CES-D <sup>a</sup> , DSST <sup>b</sup> , HVLTR-R <sup>b</sup> & SLFT <sup>b</sup>	X <sup>a</sup>	X <sup>b</sup>	X <sup>ab</sup>		X <sup>ab</sup>		X <sup>ab</sup>
10. Assess physical disability - LIFE Disability Questionnaire	X		X	X	X	X	X
11. Assess physical function - Walk test and grip strength		X		X		X	X
12. Clinical event reporting - Questionnaire & medical record review		X	X	X	X	X	X
13. MRI and Retinal Vascular Imaging in ENVIS-ion participants		X			X		
14. Additional cognitive function tests for ENVIS-ion (Stroop, Color Trails)		X			X		

Table 1. ASPREE Measurement and Study Activity Schedule (Rows 1-12)  
Additional measurements for ENVIS-ion participants (Rows 13 & 14)

Abbreviations: 3MS = Modified Mini-Mental State Examination; CES-D = Center for Epidemiologic Studies – Depression questionnaire; DSST = Digit Symbol Substitution Test; HVLTR-R = Hopkins Verbal Learning Test – Revised; SLFT = Single Letter Fluency Test.

### **ENVIS-ion only assessments prior to randomisation**

- Review inclusion/exclusion criteria for the ENVIS-ion sub-study
- Consent for the ENVIS-ion sub-study
- Completion of an Alfred MRI Department Information Sheet and Participant Screening Record
- Brain MRI, Retinal Imaging
- Stroop test, Color Trails test

### **ENVIS-ion only determinations at year 3 annual ASPREE visit**

- Completion of an Alfred MRI Department Information Sheet and Participant Screening Record
- Brain MRI, Retinal Imaging
- Stroop test, Color Trails test

#### **5.1 Brain MRI**

A non-invasive Magnetic Resonance Imaging (MRI) examination will be performed at either the Alfred or the Canberra Hospitals during the first visit and 3 years later. A number of MRI images will be used to assess various aspects of the subject's brain. First a localiser scan will be performed to orient the participant in the scanner followed by a FLAIR image that is used to assess inflammation in the cortical (surface) tissues of the brain. A T1 and T2 image will then be taken to assess brain structure volumes followed by an ASL (Arterial Spin Labelling) and associated EPI T2 scan that allows us to determine blood flow in the cortical structures. The last scan is a DTI (Diffusion Tensor Imaging) scan that allows us to determine some features of the microstructure of the cortex. In this case this scan is used to detect the presence of existing small strokes or deep infarcts.

**Analysis** - From the above scans the following information will be calculated. White Matter Hyperintensities (WMH) will be assessed with respect to their total volume and rate of change in volume. The presence or absence of sub-cortical infarction will be determined as well as the total brain volume calculated. The presence and count of cerebral microbleeds will be determined from the DTI data and brain tissue perfusion from the ASL scans. Volumetric change of structures including the hippocampus and ventricles will be assessed via the automated comparison of each of the individuals to average models of anatomy. All of the image analysis will be performed at the Dementia Collaborative Research Centre (DCRC2) Imaging Laboratory in Canberra.

## 5.2 Retinal Vascular Imaging

**Retinal photography** - All participants will have standardized non-mydratric retinal photography. After 5 minutes of dark adaptation, colour retinal photographs will be taken without pharmacological pupil dilation using Canon NMR 45 digital fundus cameras.

Two retinal photographs each centred on the optic disc (ETDRS standard fields 1) and macula (standard field 2) respectively, will be taken from both eyes of each consented participant. The retinal photography will take 10 and 15 min.

**Retinal vascular signs assessment** - The photographs will be sent to the Retinal Vascular Imaging Centre in Melbourne for analysis. Photographs centred on the optic disc of each eye will be examined using standard computer-assisted retinal analysis software that was initially developed for the ARIC study.<sup>4</sup> The grading approach measures retinal vessel diameters and combines the measurements into central retinal arteriolar and venular equivalents (CRAE and CRVE) with formulas adjusting for branching, following Parr and Hubbard formulae.<sup>4</sup>

The software has now been modified and improved<sup>5</sup> and used in a number of studies, including the AusDiab and the Blue Mountains Eye studies in Australia. In brief, the graders will, using an automated system, measure the calibres of all arteriolar and venular branches crossing a zone defined as the region from  $\frac{1}{2}$  to 1 disc diameter from the optic disc. The grader will monitor the whole process, carefully select appropriate vessel regions for calibre measurement and correctly identify small arteriolar and venular branches. Correction factors are used in analysis of the measured values of absolute vessel calibre.

The qualitative presence of focal retinal arteriolar narrowing, arteriovenous nicking, arteriolar wall opacity and the presence of retinopathy lesions will be assessed. Each lesion is classified as definite, questionable/ probable, or none in each of the retinal photographic fields. The grading will be performed by trained retinal photographic graders at RetVIC with supervision and adjudication provided. Inter- and intra-grader reliability will be assessed in a sub-sample of images.

## 5.3 Additional Cognitive Tests

**The Stroop test (Victoria Version)**<sup>6,7</sup> involves showing words that are the names of colours, although the actual words are printed in a colour of ink different from the colour name they represent. This test measures mental flexibility.

**The Color Trails**<sup>8</sup> is a non-language based test of cognitive function and requires the participant to track coloured numbers on paper, in a particular order.

## **6. NUMBER OF SUBJECTS WITH STATISTICAL VALIDATION**

Approximately 300 participants in Melbourne will be enrolled in the ENVIS-ion sub-study along with approximately 300 participants from the ACT. This will bring a combined total of VIC and ACT participants to 600 and over.

Sample size calculations are based on:

- (1) Pilot data (*CIA*) from the OPTIMA study of 144 older adults (baseline median age of 74 years), acceptance of MR imaging at 88% and MR imaging estimates of change in relevant structural brain parameters over a two-year period;
- (2) Rate of change of WMH over 3 years from the PROSPER trial of 75 year-olds (265 treated versus 270 controls) <sup>9</sup> ;
- (3) Cautious interpretation of the report by Sato et al <sup>10</sup> in which treatment with around 300 mg/day of aspirin over one year reduced incident SBIs on MRI from 20.6% to 9.6% in 150 participants with non-valvular atrial fibrillation (i.e. a relatively higher risk group than ENVIS-ion).

Based on power calculations related to the primary hypothesis, we conservatively estimate the need for at least 230 per treatment arm to achieve a statistical power of 0.9 to show a 15% difference

## **7. METHODS BY WHICH SUBJECTS WILL BE RECRUITED**

*(described in detail in the ASPREE protocol)*

**Participant identification** - All ASPREE participants who have no known contraindications to MRI are deemed eligible for entry into the ENVIS-ion sub-study. At the ASPREE screening visit subjects will be approached for participation in the ENVIS-ion sub-study.

Inclusion criteria are as for the ASPREE study with the additional exclusion criteria being absolute contraindications to undergo MRI which includes participants with any metal implants or devices. Prior to the MRI scan, each participant must be screened and approved by a Radiologist.

## **8. ESTIMATED DURATION OF STUDY**

The study is expected to last for 5 years between January 2008 and December 2012. Should additional funding be secured, the study may extend to a 5-year timepoint of MRI, RVI and additional cognitive function measurements.

## **9. FUNDING OF ENVIS-ION**

The National Health & Medical Research Council funded the ENVIS-ion study for 5 years from 2008-2012 (project grant #471460).

## **10. DATA ANALYSIS**

Group descriptive statistics will be used to define the baseline characteristics of subjects randomised to aspirin and placebo groups. Changes in continuous variables (both MRI and RVI) will be analysed using analysis of covariance (ANCOVA) adjusting for baseline values. Continuous variable changes will be normalised prior to analysis. Non-parametric methods will be used where required. Correlation and regression analysis will be used to determine the association between changes in MRI and RVI measures. Generalised linear models will be developed to determine whether age, gender and hypertensive status modify the treatment effects on MRI and RVI outcome measures. Chi-square and logistic regression analysis will be used to assess changes in categorical variables over the study period.

## **11. PROCEDURES DIFFERING FROM PREVIOUS ROUTINE CLINICAL PRACTICE/MANAGEMENT OF PATIENT**

This study is a clinical trial with specific aims. It is not related to normal care provided at the Canberra or Alfred Hospitals.

## **12. TERMINATION CRITERIA**

*(described in detail in the ASPREE protocol)*

### **12.1 Circumstances in which an individual would be withdrawn from the study by the Investigator.**

As the aim of the study is to assess ultimate outcome following randomisation to one of the treatment arms, attending physicians will be strongly encouraged to continue participants in the study. However, it is recognised that situations will arise that will necessitate withdrawal of a participant from the study. Such situations include a participant's desire to withdraw, an attending physician decision to withdraw the participant, and a transfer of participant to another physician who is not willing to participate in the study.

The occurrence of a nonfatal endpoint is not a condition for withdrawal. The first non-fatal endpoint suffered by any participant will be the primary outcome variable, but outcome will also be assessed in terms of subsequent fatal endpoints which will be included in the analysis of mortality.

In general there will be no specific withdrawal criterion relating to adverse effects of drug therapy as the analysis will be on an intention-to-treat basis. If a participant withdraws or is removed from the study for any reason, the reason for and date of the discontinuation and date of the last dose of study medication should be recorded in the appropriate section of the Subject Exit Case Report Form.

The participant may discontinue study medication but not withdraw from the study. In this case, the participant will be asked to attend study visits and every effort should be made to ensure all procedures and evaluations are performed as per the study schedule. Participants will be informed that their discontinuing in the study will not prejudice their future relations with The Alfred Hospital or The Canberra Hospital.

### **12.2 Circumstances in which the entire project would be terminated (if applicable).**

The ENVIS-ion study is a sub-study of the ASPREE clinical trial which is a major international clinical study and supported by several government and non-government organisations. Its governance framework has been well structured with a sustainable financial plan. We do not anticipate any major disaster that could have such serious impact on the entire project.

## **13. MONITORING**

An independent data and safety monitoring board, chaired by Professor Lindon Wing, has been established for ASPREE and ENVIS-ion to monitor safety and efficacy aspects of the study.

## **14. DISSEMINATION OF PROJECT RESULTS**

***(described in detail in the ASPREE protocol)***

The ENVIS-ion study will follow the written dissemination policy of the ASPREE study. This will

- Increase awareness of the ASPREE trial results by dissemination of information via repetitive messages through scientific and professional channels.
- Provide physicians, physicians' assistants or nurse practitioners with cues to action by distribution of office posters, prescription cards, and other educational materials.

The following represents various strategies to disseminate study findings and recommendations.

- **Web site:** A web site will provide information to the professional and scientific community as well as to the public regarding study results and recommendations. The web site will consist of published journal articles, newsletters, frequently asked questions (FAQs) section, links to appropriate web sites, and downloadable information for PDAs.
- **Publications:** Study findings and recommendations will be published in appropriate scientific journals to be made available to the scientific community.
- **Slide presentations:** Slide sets will be constructed to provide study rationale design, results, and implications. These will be available for formal presentations, office or departmental seminars, grand rounds, or local medical society meetings. Select slide sets, i.e. major outcomes, will be available in other languages. Slides will be accessible via the study web site. A set of slides will also be developed for presentation to consumers.
- **Formulary systems approach:** Pre-identified formulary systems will receive a summary of study findings, recommendations, relevant articles, cost-effectiveness information, and strategies for implementation to improve care.
- **Clinical guidelines:** Recommendations in guidelines will assist the facilitation of the dissemination intervention. For example, the ASPREE study results may be reinforced by the existing US Preventive Task Force and American Heart Association guidelines for the evaluation, prevention and management of cardiovascular disease in adults.
- **Education Materials:** Development of physician office posters, reference cards, and consumer brochures will be effective tools for disseminating study findings and recommendations. Office posters and reference cards will assist physicians in management. Consumer brochures will educate the public and provide the necessary information to encourage consumers to speak to their physician regarding their management.

## **15. PRODUCT LIABILITY**

The ENVIS-ion study is not sponsored by a pharmaceutical company. Bayer HealthCare have agreed to provide a Product Liability statement for each batch of the study drug: aspirin (100 mg enteric-coated) or placebo.

## **16. REPORT OF PROJECT**

The ENVIS-ion study research team will provide a statement to the Alfred Hospital Ethics Committee and ACTHREC annually or as required. When the research is completed, published papers and abstracts will inform the Ethics Committees of the outcome.

## **17. ETHICAL CONDUCT OF THE TRIAL**

This study will be conducted in accordance this protocol, ICH GCP *Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)* Annotated with TGA comments and NH&MRC *National Statement on Ethical Conduct in Human Research 2007* and in keeping with local regulations.

## **18. INFORMED CONSENT**

### **18.1 Consent Form**

Before obtaining consent from each participant, he / she must be informed of the objectives, benefits, risks and requirements of the study, as well as the nature of the test medication. An information sheet should be given to every participant prior to screening and randomisation.

Participants will be giving their own consent after having read all content of the information sheet and consent form. Participant and investigator each retain a copy of the signed consent form.

### **18.2 Obtaining Consent**

The Investigator, or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the participant of all pertinent aspects of the ENVIS-ion study including the written participant information sheet.

All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Participants are expected to giving their own consents by reading content in the information sheet and consent form and giving their signatures by themselves. In those who might have vision impairment, a research officer may read out content and ensure a thoroughly understanding of all content before asking for signature.

- Prior to a subject's participation in the study, the written Informed Consent Form should be signed, name filled in and personally dated by the participant or by the participant's legally acceptable representative, and by the person who conducted the informed consent discussion.

- A copy of the signed and dated written Informed Consent Form will be provided to the participant. The original consent is to be stored in the participant's individual study file, held by the investigator. A second copy may be filed in the participant's file at the general practice.
- The Participant information Sheet and Consent Form used for obtaining the participant's informed consent must be the current version that has been reviewed and approved by the appropriate Ethics Committee.

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