



The ASPREE Healthy Ageing Biobank



Protocol

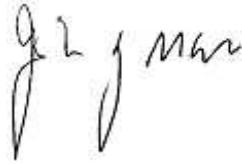
Professor John J McNeil
Principle Investigator
Department of Epidemiology and Preventive Medicine, Monash University,
Alfred Hospital, Melbourne 3004
Victoria, Australia

Dr Robyn Woods
Executive Officer
robyn.woods@med.monash.edu.au

Endorsed by



PROTOCOL SIGNATURE PAGE
Protocol Version date: 21 January, 2008



Principal Investigator:

21/01/2008

Professor John McNeil

Signature

Date

This document is confidential. The Investigator declares that they have read the final study protocol and *its appendices*. The Investigators will conduct the study according to the procedures specified in the study protocol, and in accordance with ICH GCP (annotated with TGA comments).

Name of Study Investigator _____

Signature of Study Investigator

Date

Table of Contents

1	INTRODUCTION.....	5
1.1	Summary.....	5
1.2	Background and Rationale.....	5
1.2.1	<i>Cardiovascular bio-markers.....</i>	<i>5</i>
1.2.2	<i>Dementia bio-markers.....</i>	<i>7</i>
1.2.3	<i>Cancer bio-markers.....</i>	<i>7</i>
1.2.4	<i>Bio-bank development: an international incentive.....</i>	<i>7</i>
1.2.5	<i>Summary.....</i>	<i>7</i>
2	ESTABLISHING THE BIOBANK.....	8
3	OBJECTIVE.....	9
4	STUDY POPULATION.....	9
4.1	Inclusion criterion.....	9
4.2	Participant identification	9
4.3	Participant discontinuation	9
5	BIOBANK SUPPLIES AND PROCEDURES.....	10
5.1	Blood sample collection	10
5.2	Blood sample processing and storage	10
5.3	Blood sample access and utilisation	10
5.4	Tests to be performed.....	11
5.5	Blood sample disposal	11
6	SAMPLE SIZE AND POWER CALCULATIONS.....	11
7	MEASUREMENTS, CRFs AND ANALYTICAL METHODS.....	12
7.1	Schedule of study visits.....	12
7.1.1	<i>Visit 1 (Run In), ASPREE Clinical Trial.....</i>	<i>12</i>
7.1.2	<i>Visit 2 (Randomisation), ASPREE Clinical Trial.....</i>	<i>12</i>
7.1.3	<i>Determinations via annual contact.....</i>	<i>12</i>
7.2	Case Report Forms (CRFs).....	12
7.3	Dissemination and implementation of results.....	13
8	ADHERENCE TO ETHICAL, REGULATORY AND ADMINISTRATIVE CONSIDERATIONS.....	13
8.1	Ethical Considerations.....	13
8.1.1	<i>General.....</i>	<i>13</i>
8.1.2	<i>Informed consent.....</i>	<i>14</i>
8.2	Regulatory Considerations.....	14

8.2.1	<i>Financing</i>	14
8.3	Administrative Organisation.....	15
8.3.1	<i>Individual and Committee responsibilities</i>	15
8.3.2	<i>Publication policy</i>	15
9	DATA MANAGEMENT.....	16
9.1	Data Handling and Record Keeping.....	16
9.2	Quality Control.....	16
10	LIST OF REFERENCES.....	18
	APPENDIX 1. ASPREE HEALTHY AGEING BIOBANK COMMITTEE.....	21

1 INTRODUCTION

1.1 Summary

The ASPREE Healthy Ageing Biobank is an initiative in which blood samples will be collected from healthy participants, aged 70 and over, who have provided consent to participate in the ASPREE Clinical Trial. Participants in the Biobank will be followed for a period of 5 years, and may then provide a second blood sample at the conclusion of the study. The aim of the ASPREE Healthy Ageing Biobank is to establish a repository of blood samples from which potential biomarkers in the blood and/or genes may be identified that better predict those at risk of developing cardiovascular and cerebrovascular disease, cancer or dementia. It is anticipated that during the course of the study, a proportion of the elderly population will experience an adverse medical event, which may be cardiovascular in origin (myocardial infarction, stroke), or the onset of cognitive decline/dementia, or cancer. At a time in the future and under separate application, the stored blood samples, together with other information obtained about these participants (in relation to their health, lifestyle and other circumstances) will be analysed to address specific questions regarding the association of biomarkers and these major health outcomes. This protocol focuses on the collection and storage of these samples and not on any specific analysis of biomarkers. Future applications for ethical approval will be made regarding projects that address disease outcomes of interest observed during the 5 year period of the study.

1.2 Background and Rationale

1.2.1 Cardiovascular bio-markers

Plasma cholesterol (total, plus low - and high- density lipoprotein cholesterol; LDL-C and HDL-C, respectively) and triglycerides are the conventional biomarkers used when determining a patient's level of cardiovascular risk, as recommended by the National Cholesterol Education Program's Adult Treatment Panel III.¹ However, it is now accepted that in the majority of cases, overt hyperlipidaemia alone does not adequately predict future vascular events.² Nor is the presence of one or more traditional risk factors (such as smoking, hypertension or diabetes) sufficient – the prevalence of these risk factors amongst individuals who go on to develop coronary heart disease is comparable to that seen in individuals who remain disease-free.³ Thus in recent years, an increasing amount of attention has been directed towards the discovery and establishment of additional plasma bio-markers that may predict, in

a more effective and specific manner, first ever cardiovascular events.

In this context, markers of inflammation have emerged as potential candidates for biomarkers of cardiovascular risk, consistent with the notion that atherosclerosis is effectively an inflammatory disease.⁴ Of these candidates, high-sensitivity C-reactive protein (hs-CRP) has been the most encouraging, with a number of prospective studies demonstrating that hs-CRP is an independent predictor of risk of myocardial infarction, stroke, peripheral artery disease and sudden cardiac death in healthy individuals.⁵ Furthermore, although CRP production can increase in response to multiple stimuli, its predictive capacity appears to be specific for vascular events, as elevated hs-CRP levels do not correlate with non-cardiovascular mortality, or the onset of other inflammatory disorders.⁶ The American Heart Association has incorporated hs-CRP measurements into its guidelines for the assessment of individuals considered to be at intermediate cardiovascular risk⁷, and there is currently debate as to whether this group should be expanded to include all individuals irrespective of risk level.⁸ However, it has not yet been established that a reduction in hs-CRP levels will necessarily lower vascular risk.⁹

Acute phase reactants, such as fibrinogen^{10 11}, and inflammatory cytokines¹², leukocyte adhesion molecules, soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular adhesion molecule (sVCAM), soluble P-selectin^{13 14}, markers of leukocyte activation, e.g. myeloperoxidase^{15 16} as well as markers of altered thrombosis: homocysteine¹⁷, tissue-type plasminogen activator (tPA), plasminogen activator inhibitor (PAI-1)¹⁸, markers of oxidative stress, e.g. oxidized LDL¹⁹, and protein components of HDL-C and LDL-C, apolipoproteins –A₁ (apoA₁) and –B (apoB), respectively²⁰ have all shown promise as novel cardiovascular bio-markers. However, the use of these markers in general screening has been hindered by the fact that, unlike hs-CRP², they have to date failed to provide prognostic value above and beyond that derived from global assessment algorithms such as the Framingham Risk Score.⁹

Another emerging cardiovascular bio-marker is brain-type natriuretic peptide (BNP), which is released from the myocardium in response to myocardial stretch, and is a useful tool in the diagnosis of heart failure. Recent cohort studies in patients with stable coronary artery disease suggest that, in addition, both BNP and the amino terminal fragment of the prohormone, NT-proBNP, are independent predictors of cardiovascular mortality, stroke²¹ and possibly myocardial infarction.²²

1.2.2 Dementia bio-markers

Considerable overlap exists between cardiovascular disease and dementia in terms of the plasma bio-markers of interest, such as homocysteine ²³, not least because atherosclerosis is associated with an increased risk of both Alzheimer's disease (AD) and vascular dementia ²⁴, and vascular abnormalities are often found in brains of patients with AD.²⁵ Studies have linked late-onset AD with elevated plasma levels of apolipoprotein E (apoE) ²⁶, and the genetic expression of the apoE e4 isoform.²⁷ Recent evidence also suggests the ratio of amyloid precursor proteins A β 42/40 is a predictive bio-marker of AD in patients with mild cognitive impairment.²⁸

1.2.3 Cancer bio-markers

Observational, retrospective studies to date have investigated the relationship between markers of tumoral angiogenesis, such as microvessel density and vascular endothelial growth factor (VEGF) expression, and recurrence/overall survival rates in patients with colorectal cancer.^{29 30} However, prospective studies of putative cancer bio-markers are limited, hence there is a clear need to identify novel bio-markers that may predict cancer incidence in a primary setting. This is a rapidly evolving area of research.

1.2.4 Bio-bank development: an international incentive

There is growing and substantial international interest in the benefits derived from the use of bio-banks for discovering new biomarkers and predictors of disease. The US National Institutes of Health has undertaken a most rigorous review of this emerging field of medical research, and considers it so worthwhile that it has invested millions of dollars in the continued development and expansion of its bio-banks: in 2006 it launched two new initiatives, the Genetic Association Information Network, and the Genes & Environment Initiative.³¹ There is also ongoing development of the UK Biobank, while similar projects are being conducted in Sweden and Japan. It would be advantageous to add to this global wealth of genetic and proteomic information with an Australian-specific cohort.

1.2.5 Summary

The ASPREE Clinical Trial will be used as the basis for establishing a bio-bank of blood samples from healthy elderly participants. These samples will be able to provide biological information that can be linked with the ongoing collection of clinical data relating to participants' health, lifestyle and other circumstances. The biomarkers outlined are currently of interest and it is likely that over the duration of the study new biomarker targets will be identified.

2 ESTABLISHING THE BIOBANK

Patients who have been invited to participate in the ASPREE Clinical Trial and who satisfy the inclusion/exclusion criteria at phone screening, will be asked to meet with an ASPREE research nurse at their local GP's practice for Visit 1 (run-in). At this visit, patients will have the ASPREE study explained to them and if they provide consent to participate in the Clinical Trial, they will also be given the Patient Information and Consent Form (PICF) regarding the ASPREE Healthy Ageing Biobank. Participation in the ASPREE Clinical Trial does not mean the patient is obliged to also enter the Biobank study. Informed consent for participation in the ASPREE Healthy Ageing Biobank will be sought at ASPREE Clinical Trial Visit 2, at the relevant ASPREE regional centre (eg. for metropolitan Melbourne: this will be the Department of Epidemiology & Preventive Medicine, Monash University, Clinical Trials Centre (CTC), Caulfield General Medical Centre). Non-fasting blood samples will then be collected from consenting patients during this visit. This will add about 15 minutes to the length of the visit, so that in total Visit 2 will take up about an hour of the patient's time.

Patients cannot take part in the Biobank unless they have agreed to participate in the Clinical Trial. However, those participants who consent to providing a blood sample for the Biobank, and who do not ultimately proceed in the ASPREE Clinical Trial for whatever reason (e.g. withdrawn consent) can remain participants in the ASPREE Biobank.

In consenting to providing a blood sample for the ASPREE Biobank, the participant may choose to allow their blood sample to be analysed for biomarkers (e.g. proteins) and/or genetic material. The research nurse, or a trained phlebotomist, will collect the blood sample, or provide a request form for blood sample collection at a registered Pathology Provider. This baseline blood sample will be collected prior to the participant being randomised to a treatment arm and receiving their study medication for the ASPREE Clinical Trial, which occurs at the conclusion of Visit 2 with the research nurse.

ASPREE Biobank participants will be followed up for 5 years, in the same manner as participants involved only in the ASPREE Clinical Trial. For those participants who are no longer involved in the Clinical Trial but who choose to remain participants in the Biobank, follow-up may be achieved by annual contact (without the face-to-face visits with the research nurse), accessing patients' medical records (in order to capture information regarding any serious medical events that have occurred), as

well as accessing the National Death Index government database in the event of mortality, to ascertain date and cause of death.

At the end of the five year period, participants will be invited to take part in an ongoing extension study, to enable long-term follow-up. Participants may also be asked to provide another 30 – 40 mL blood sample at that time.

3 OBJECTIVE

The main objective of the ASPREE Healthy Ageing Biobank is to establish a repository of blood samples that will be available for the future assessment of blood biomarkers (proteins and/or genes). that better predict individuals at risk of developing cardiovascular and cerebrovascular disease, cancer or dementia.

4 STUDY POPULATION

4.1 Inclusion criterion

The inclusion criterion for participation in the ASPREE Healthy Ageing Biobank is the provision of consent to participate in the ASPREE Clinical Trial (RACGP NREEC 02/22b).

4.2 Participant identification

All patients attending their GP's practice for Visit 1 of the ASPREE Clinical Trial will be invited to provide consent for an additional blood sample for the ASPREE Biobank.

4.3 Participant discontinuation

If a participant withdraws from the ASPREE Biobank study for any reason, the participant will be asked to sign a Revocation of Consent Form. The date of the discontinuation should be recorded in the appropriate section of the Subject Exit Case Report Form (CRF).

Where a participant chooses to withdraw from the ASPREE Clinical Trial, this may not necessarily impact directly upon their involvement in the Biobank study, as separate Consent forms are signed to acknowledge participation in each of these ASPREE studies. The participant may chose to revoke consent for the ASPREE Clinical Trial but still remain in the ASPREE Biobank.

5 BIOBANK SUPPLIES AND PROCEDURES

5.1 Blood sample collection

The blood collection involves taking 30 – 40 mL of blood from the antecubital vein will be collected into 2 – 3 EDTA (purple, 9.0ml) and one Serum gel (brown, 7.5ml) tubes. The blood collection procedure will follow Standard Operating Procedures for the Collection of Blood Samples of the local institution.

After the sample has been collected, the time of blood collection is recorded, and the participant's name and any identifying features replaced with the same Subject Identification Number that has been assigned to the participant for the Clinical Trial.

5.2 Blood sample processing and storage

The Standard Operating Procedures for the ASPREE Healthy Ageing Biobank describe the blood sample processing and storage procedures in more detail. Briefly, blood samples will be processed at the particular ASPREE regional centre or Pathology centre at which collection has taken place, and transported if necessary (i.e. where the collection / processing site is not the Clinical Trials Centre (CTC), Caulfield General Medical Centre) to the CTC for short-term storage, in accordance with the Standard Operating Procedures for the ASPREE Healthy Ageing Biobank. Additional sites at the Alfred, the Ludwig Institute for Cancer Research, or other locations at Monash may be utilised in the future for long-term storage. Wherever possible, blood samples will be processed into the following components for long term storage: Guthrie card, blood pellet, buffy coat, plasma and serum. Bloods should ideally be processed and placed in frozen storage within 2 hours of collection.

Labelled cryovials will be stored in vapour phase, high capacity nitrogen storage tanks or -80°C freezers for an indefinite period, in accordance with the Standard Operating Procedures for the ASPREE Healthy Ageing Biobank.

5.3 Blood sample access and utilisation

A governance structure will be established to ensure the ethical handling of stored blood samples. Researchers wishing to access and test blood samples for biomarkers and/or genes of interest will not be permitted to do so until they have obtained approval from the ASPREE Healthy Ageing Biobank Committee to conduct their research. Applicants will be judged on the scientific merit of their proposed studies and the availability of sufficient funding to carry out the project. Accurate records of the aliquots of each stored blood sample will be achieved through the use

of a Nunc Next Generation CryoTube Scanner and software (refer to Standard Operating Procedures for the ASPREE Healthy Ageing Biobank). These will be utilised on each occasion that a sample is either stored, or retrieved for access by an approved researcher.

5.4 Tests to be performed

Biomarker tests to be performed may include, but are not limited to, measurements of plasma and serum levels of any of the following:

BNP, NT-proBNP; myeloperoxidase; D-dimer; Matrix Metalloproteinase-9 (MMP-9); adiponectin; cystatin C; hs-CRP, lipids (total cholesterol, LDL-C, HDL-C, triglycerides), ApoA₁, ApoB, ApoE, lipoprotein(a), oxidised LDL; fibrinogen; homocysteine; serum amyloid A; amyloid precursor proteins A β 42 and A β 40; vitamin B12, folate; soluble CD40 ligand, troponin -I, -T; lipoprotein-associated phospholipase A₂; adrenomedullin; vasopressin; neopterin; tissue inhibitor of metalloproteinases -1, -2; leptin; interleukin -1, -6, -10, -18; sICAM, sVCAM, soluble P-selectin; tPA, PAI-1; VEGF -B, -C, -D; platelet-derived growth factor (PDGF) -AA, -AB, -BB; tumor necrosis factor (TNF)- α ; insulin-like growth factor (IGF) -I, -II.

Genetic marker testing to be performed may include, but is not limited to, analysis of any of the following:

ApoE (e2/e3/e4 alleles), ApoA₁, ApoB; fibrinogen; LDLR; CYP7A1; PON1; SREBF1; CETP; MTP; ABCG5, ABCG8; HMGCR; MMP-3; ACE; aldosterone synthase; Ang II AT1R; eNOS; interleukin -1 β , -6; TLR4.

5.5 Blood sample disposal

Blood samples, or portions thereof, that are not ultimately used for biomarker or genetic marker analysis will be disposed of by the ASPREE Biobank as bio-hazardous waste in the appropriate manner, according to the Waste Disposal guidelines of the local institution.

6 SAMPLE SIZE AND POWER CALCULATIONS

A sufficient number of events in the health areas of interest are expected to occur in the 10,000 participants over the course of the five years of collecting blood samples for the ASPREE Healthy Ageing Biobank to enable statistically significant differences to be determined. These are: 1180 for cardiovascular disease (based on an average of 23.6 events/1000 person-years), 1275 for dementia (25.5 events/1000 person-years) and 435 for all cancers (8.7 events/1000 person-years).

Regarding the analysis of specific blood proteins and genetic material, the statistical tests employed will relate to the disease biomarkers of interest, and the individual scientific proposal seeking access to the blood samples. In general, however, Pearson correlation co-efficients will be calculated to determine whether there is a significant relationship between levels of certain blood proteins, or alterations in genetic material, and the incidence of a particular disease (cardiovascular, dementia or cancer) or significant medical event in participants.

7 MEASUREMENTS, CRFs AND ANALYTICAL METHODS

7.1 Schedule of study visits

7.1.1 Visit 1 (Run-in), ASPREE Clinical Trial

- a) Provide the participant with the ASPREE Healthy Ageing Biobank Participant Information & Consent Form (PICF) (only if the participant has consented to participation in the ASPREE Clinical Trial).

7.1.2 Visit 2 (Randomisation), ASPREE Clinical Trial

- a) In participants who provide consent to participate in the ASPREE Biobank: collect a non-fasting blood sample, or provide a request form for blood sample collection at a registered Pathology Provider. (N.b. If the latter, the research nurse will need to obtain confirmation that a blood sample has been collected, before then randomizing the participant and dispensing their ASPREE Clinical Trial medication).

7.1.3 Determinations via annual contact

- a) Vital status.
- b) Medical events (cardiovascular, dementia or cancer-related) by patient and investigator report and a search of the practice held medical record.

7.2 Case Report Forms (CRFs)

CRFs, such as the Adverse Events and Serious Adverse Events CRFs, are used to record details about adverse medical events (e.g. cardiovascular, dementia or cancer-related) that occur and are an integral part of the ASPREE Biobank study and subsequent reports. The CRFs, therefore, must be legible and complete. All forms must be filled in using a black ballpoint pen and errors must be crossed out but not obliterated and the corrections must be written above or beside error on a free space.

All corrections must be initialed and dated.

At the end of the ASPREE Biobank study, the investigator must sign a Final Investigator's Statement confirming that all data were checked for accuracy and completeness.

CRFs must be kept current to reflect the participant's course throughout the study. Participants are not to be identified on the CRF by name. Appropriate coded information (i.e. Subject Identification Number) and participant initials must be used. The research nurse must keep a separate confidential record of full patient details (Subject Identification Log) to permit identification of all participants enrolled in the study to ensure case follow-up if required. Information linking patients' details with their Subject Identification Number is also stored on the ASPREE database.

7.3 Dissemination and implementation of results

The following represents various strategies to disseminate ASPREE Healthy Ageing Biobank study findings and recommendations.

- *Web site.* The ASPREE 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.
- *Publication.* 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. Slides will be accessible via study web site. A set of slides will also be developed for presentation to consumers.

8 ADHERENCE TO ETHICAL, REGULATORY AND ADMINISTRATIVE CONSIDERATIONS

8.1 Ethical Considerations

8.1.1 General

The ASPREE Healthy Ageing Biobank will be established in accordance with this protocol, current ethical guidelines (e.g. ICH GCP notes 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).

The principal investigator at each ASPREE Regional Site may be required to submit the ASPREE Healthy Ageing Biobank protocol to their institution's Ethics Committee and obtain approval prior to commencing the study. It is the responsibility of the ASPREE Regional Lead Investigator to determine their own institution's policies.

The ASPREE Clinical Trial has been approved by the Royal Australian College of General Practitioners Ethics Committee – National Research and Evaluation Ethics Committee (RACGP NREEC 02/22b), Monash University Standing Committee for Ethics in Research Involving Humans (2006/745MC), and the University of Tasmania Human Research Ethics Committee (H0008933).

8.1.2 Informed Consent

The research nurse or 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 ASPREE Healthy Ageing Biobank, including the objectives, benefits, risks and requirements of the study. All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

- a) Prior to a patient's participation in the study, the written ASPREE Biobank Patient Information & Consent Form (PICF) should be signed, the box(es) corresponding to the use of blood samples for protein and/or genetic testing checked as appropriate, the patient's name filled in and personally dated by the patient or, by the witness to the patient's signature, and by the researcher who conducted the informed consent discussion. A copy of the signed and dated written PICF will be provided to the patient. The original consent form 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 ASPREE Biobank PICF used for obtaining the patient's informed consent must be the current version that has been reviewed and approved by the appropriate Ethics Committee.

- b) All participants must give their informed consent **before** their blood sample is collected (and prior to randomization, at Visit 2).

8.2 Regulatory Considerations

8.2.1 Financing

The ASPREE Healthy Ageing Biobank is supported by the CSIRO. ASPREE has received project grants from the National Health and Medical Research Council and National Heart Foundation of Australia, and an educational grant from Bayer HealthCare.

8.3 Administrative Organisation

8.3.1 Individual and Committee responsibilities

(Membership details provided in Appendix 1)

Lead investigator (John McNeil), study director (Christopher Reid) and executive officer (Robyn Woods).

Overall management of the ASPREE Health Ageing Biobank, and the Biobank laboratory, coordination of the ASPREE Regional Centres, and coordination of all aspects of the ASPREE Healthy Ageing Biobank.

ASPREE Healthy Ageing Biobank Committee

Responsibility for the protocol and any changes to said, for the general running and financial management of the Biobank, and for the future reviewing of applications from scientists seeking to access and conduct research on samples stored in the Biobank.

8.3.2 Publication policy

This policy covers all publications and abstracts originating from ASPREE and any sub-study (including the ASPREE Healthy Ageing Biobank). The report of the paper will follow the CONSORT (Consolidated Standards of Reporting Trials) guidelines for reporting randomised controlled trials.³²

Authorship. - Manuscripts and abstracts relating to the ASPREE Healthy Ageing Biobank must include all current members of the ASPREE Healthy Ageing Biobank Committee using the following formula:

- All publications will be on behalf of “the ASPREE Study Group”.
- A writing committee will be established for each publication from which a lead author will be identified and responsible for the initial draft of the manuscript
- The lead author will be the first author of the publication
- Subsequent author(s) from the writing committee will be listed according to the amount of input to the writing of the paper.
- All other contributors in last name alphabetical order.
- Members of the ASPREE Healthy Ageing Biobank Committee will be named in

- the description of the ASPREE Study Group in each manuscript
- All GP Co-investigators and sub-committee members will be listed on the ASPREE web-site and acknowledged in every publication.

Non-Biobank Committee authors utilise the same formula. Disputes about authorship must be notified to the study director to be resolved at the next meeting of the ASPREE Healthy Ageing Biobank Committee.

Drafts -Initial and major upgraded manuscripts and abstracts must be circulated to all members of the ASPREE Healthy Ageing Biobank Committee and any other Committee within ASPREE where relevant. Members have a maximum of one week to send responses.

9 DATA MANAGEMENT

9.1 Data Handling and Record Keeping

All the results from medical evaluations conducted during the ASPREE Biobank study will be recorded in an appropriate Case Report Form (CRF) for each participant and filed in the relevant ASPREE regional coordinating centre. Copies of these CRFs will be transferred to the Data Management Centre (DMC) where they will be scanned into the ASPREE Clinical Trial database.

Full identification of each participant will be kept by the investigator who should agree to supply all details to the auditor and/or the Regulatory Authorities if required. All information will be treated in accordance with professional conduct. All corrections and alterations of data on the CRFs must be made according to the instructions provided, and must be dated and signed. The research staff will fill out or correct the CRFs, in consultation with the investigator. The CRFs must be completed after each annual telephone call to the participant, if necessary (or as soon as all data is available to confirm the occurrence of the medical event, e.g. hospital records) and sent via fax to a Toll free number at the DMC.

At the end of the ASPREE Biobank study the Investigator must verify the completeness of the data collection by signing the CRFs. These forms will then be sent to the DMC for filing and eventual archiving.

9.2 Quality Control

All regional centres participating in the ASPREE Biobank study are required to make available source documents for study-related monitoring visits. When possible, State initiation meetings will occur between members of the DMC, the study director,

regional coordinators, study nurses, investigators, and administrative staff. Each of the State Centres will be randomly monitored by DMC staff for source document verification and signed informed consent forms in addition to knowledge of, and compliance with, protocol requirements. All data collected at monitoring visits will be treated strictly as confidential. During said monitoring visits, monitors will:

- a) Meet the members involved in the study.
- b) Ensure that the site, the facilities and the materials used in the study are acceptable for the conduct of the study.
- c) Verify that the study is being conducted in accordance with the protocol and ICH/GCRP guidelines.
- d) Review study-related documentation and correspondence.
- e) Ensure that the correct version of the consent form was signed by the participant prior to any study-related procedures.
- f) Confirm that the participants meet eligibility criteria
- g) Directly access a sample source of documents for comparison with data in the CRFs and check that the CRFs have been completed correctly and accurately.
- h) Check completion of blood sample access & utilisation logs at the site where blood samples are stored.
- i) Document all site monitoring visits.

10 LIST OF REFERENCES

1. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA* 2001;**285**:2486-2497.
2. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 2002;**347**:1557-1565.
3. Greenland P, Knoll MD, Stamler J, Neaton JD, Dyer AR, Garside DB, Wilson PW. Major risk factors as antecedents of fatal and non-fatal coronary heart disease events. *JAMA* 2003;**290**:891-897.
4. Ross, R. Atherosclerosis – an inflammatory disease. *N Engl J Med* 1999;**340**:115-126.
5. Torres JL and Ridker PM. Clinical use of high-sensitivity C-reactive protein for the prediction of adverse cardiovascular events. *Curr Opin Cardiol* 2003;**18**:471-478.
6. Tice JA, Browner W, Tracy RP, Cummings SR. The relation of C-reactive protein levels to total and cardiovascular mortality in older U.S. women. *Am J Med* 2003;**114**:199-205.
7. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, Rifai N, Smith SC Jr, Taubert K, Tracy RP, Vinicor F. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003;**107**:499-511.
8. Ridker PM. C-reactive protein and the prediction of cardiovascular events among those at intermediate risk. *J Am Coll Cardiol* 2007;**49**:2129-2138.
9. Ridker PM, Brown NJ, Vaughan DE, Harrison DG, Mehta JL. Established and emerging plasma biomarkers in the prediction of first atherothrombotic events. *Circulation* 2004;**109**:IV6-IV19.
10. Jenny NS, Yanez ND, Psaty BM, Kuller LH, Hirsch CH, Tracy RP. Inflammation biomarkers and near-term death in older men. *Am J Epidemiol* 2007;**165**:684-695.
11. Ma J, Hennekens CH, Ridker PM, Stampfer MJ. A prospective study of fibrinogen and risk of myocardial infarction in the Physicians' Health Study. *J Am Coll Cardiol* 1999;**33**:1347-1352.
12. Blankenberg S, Luc G, Ducimetiere P, Arveiler D, Ferrieres J, Amouyel P, Evans A, Cambien F, Tiret L. Interleukin-18 and the risk of coronary heart disease in European men: the Prospective Epidemiological Study of Myocardial Infarction

(PRIME). *Circulation* 2003;**108**:2453-2459.

13. Ridker PM, Hennekens CH, Roitman-Johnson B, Stampfer MJ, Allen J. Plasma concentration of soluble intercellular adhesion molecule 1 and risks of future myocardial infarction in apparently healthy men. *Lancet* 1998;**351**:88-92.

14. Varughese GI, Patel JV, Tomson J, Blann AD, Hughes EA, Lip GY. Prognostic value of plasma soluble P-selectin and von Willebrand factor as indices of platelet activation and endothelial damage/dysfunction in high-risk patients with hypertension: a sub-study of the Anglo-Scandinavian Cardiac Outcomes Trial. *J Intern Med* 2007;**261**:384-391.

15. Meuwese MC, Stroes ES, Hazen SL, van Miert JN, Kuivenhoven JA, Schaub RG, Wareham NJ, Luben R, Kastelein JJP, Khaw KT, Boekholdt SM. Serum myeloperoxidase levels are associated with the future risk of coronary artery disease in apparently healthy individuals. *J Am Coll Cardiol* 2007;**50**:159-165.

16. Zhang R, Brennan ML, Fu X, Aviles RJ, Pearce GL, Penn MS, Topol EJ, Sprecher DL, Hazen SL. Association between myeloperoxidase levels and risk of coronary artery disease. *JAMA* 2001;**286**:2136-2142.

17. Wald DS, Law M, Morris JK. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. *BMJ* 2002;**325**:1202-1208.

18. Thogersen AM, Jansson JH, Boman K, Nilsson TK, Weinehall L, Huhtasaari F, Hallmans G. High plasminogen activator inhibitor and tissue plasminogen activator levels in plasma precede a first acute myocardial infarction in both men and women: evidence for the fibrinolytic system as an independent primary risk factor. *Circulation* 1998;**98**:2241-2247.

19. Nordin Fredrikson G, Hedblad B, Berglund G, Nilsson J. Plasma oxidised LDL: a predictor for acute myocardial infarction? *J Intern Med* 2003;**253**:425-429.

20. Clarke R, Emberson JR, Parish S, Palmer A, Shipley M, Linksted P, Sherliker P, Clark S, Armitage J, Fletcher A, Collins R. Cholesterol fractions and apolipoproteins as risk factors for heart disease mortality in older men. *Arch Intern Med* 2007;**167**:1373-1378.

21. Omland T, Sabatine MS, Jablonski KA, Rice MM, Hsia J, Wergeland R, Landaas S, Rouleau JL, Domanski MJ, Hall C, Pfeffer MA, Braunwald E. Prognostic value of B-type natriuretic peptides in patients with stable coronary artery disease. The PEACE trial. *J Am Coll Cardiol* 2007;**50**:205-214.

22. Bibbins-Domingo K, Gupta R, Na B, Wu AH, Schiller NB, Whooley MA. N-terminal fragment of the prohormone brain-type natriuretic peptide (NT-proBNP), cardiovascular events, and mortality in patients with stable coronary heart disease. *JAMA* 2007;**297**:169-176.

23. Seshadri S, Beiser A, Selhub J, Jacques PF, Rosenberg IH, D'Agostino RB, Wilson PW, Wolf PA. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. *N Engl J Med* 2002;**346**:476-483.
24. Hofman A, Ott A, Breteler MM, Bots ML, Slooter AJ, van Harskamp F, van Duijn CN, van Broeckhoven C, Grobbee DE. Atherosclerosis, apolipoprotein E and prevalence of dementia and Alzheimer's disease in the Rotterdam study. *Lancet* 1997;**349**:151-154.
25. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. *Lancet* 2001;**357**:169-175.
26. Taddei K, Clarnette R, Gandy SE, Martins RN. Increased plasma apolipoprotein E (apoE) levels in Alzheimer's disease. *Neurosci Lett* 1997;**223**:29-32.
27. Orsitto G, Seripa D, Panza F, Franceschi M, Cascavilla L, Placentino G, Matera MG, Paris F, Capurso C, Solfrizzi V, Dallapiccola B, Pilotto A. Apolipoprotein E genotypes in hospitalised elderly patients with vascular dementia. *Dement Geriatr Cogn Disord* 2007;**23**:327-333.
28. Hansson O, Zetterberg H, Buchhave P, Andreasson U, Londos E, Minthon L, Blennow K. Prediction of Alzheimer's disease using the CSF Abeta42/Abeta40 ratio in patients with mild cognitive impairment. *Dement Geriatr Cogn Disord* 2007;**23**:316-320.
29. Des Guetz G, Uzzan B, Nicolas P, Cucherat M, Morere JF, Benamouzig R, Breau JL, Perret GY. Microvessel density and VEGF expression are prognostic factors in colorectal cancer. Meta-analysis of the literature. *Br J Cancer* 2006;**94**:1823-1832.
30. Tamura M, Oda M, Tsunozuka Y, Matsumoto I, Kawakami K, Watanabe G. Vascular endothelial growth factor expression in metastatic pulmonary tumor from colorectal carcinoma: utility as a prognostic factor. *J Thorac Cardiovasc Surg* 2004;**128**:517-522.
31. Tilstone C. Further plans announced for national biobanks. *Lancet Oncol* 2006;**7**:195-196.
32. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *Clin Oral Invest* 2003;**7**:2-7.

APPENDIX 1.

ASPREE HEALTHY AGEING BIOBANK COMMITTEE

Professor John J McNeil MBBS FRACP
MSc PhD FAFPH
Head of Department of Epidemiology and
Preventive Medicine
Monash University / Alfred Hospital,
Melbourne 3004
john.mcneil@med.monash.edu.au

Dr Trevor Lockett, PhD
Theme Leader,
CSIRO
Preventative Health National Research
Flagship
North Ryde, NSW 2113
Trevor.lockett@csiro.au

Dr Robyn Woods BSc(Hon) PhD
Senior Research Fellow
Executive Officer, ASPREE
Department of Epidemiology and
Preventive Medicine
Monash University / Alfred Hospital
Melbourne 3004
robyn.woods@med.monash.edu.au

Professor Richard Head, PhD
Director,
Preventative Health Flagship
CSIRO
231 North Terrace
Adelaide SA 5000
Richard.head@csiro.au

Assoc Prof Chris M Reid BA DipEd MSc
PhD Cert Health Econ
Assoc Director
NHMRC Centre of Clinical Research
Excellence in Therapeutics
Department of Epidemiology and
Preventive Medicine
Monash University / Alfred Hospital
Melbourne 3004
chris.reid@med.monash.edu.au

Dr Peter Gibbs MBBS FRACP
Clinical Director,
Australian Cancer Grid
Ludwig Institute for Cancer Research
Parkville VIC
peter.gibbs@mh.org.au