

ASPIrin in Reducing Events in the Elderly



Protocol

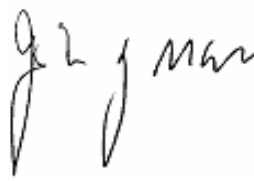
Professor John J McNeil
Department of Epidemiology and Preventive Medicine
Monash University,
Alfred Hospital, Melbourne 3004
Victoria, Australia

Dr Robyn Woods
Executive Officer
robyn.woods@med.monash.edu.au
Version 2.0: 6 March, 2008
Endorsed by



PROTOCOL SIGNATURE PAGE

Protocol Version 2.0 Date: 6 March, 2008

Principal Investigator:		06/03/2008
Professor John McNeil	<i>Signature</i>	<i>Date</i>

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	5
1.2.1	<i>Major adverse cardiovascular events</i>	5
1.2.2	<i>Cardiovascular benefit versus risk in the elderly</i>	7
1.2.3	<i>All-cause mortality</i>	8
1.2.4	<i>All-cause dementia</i>	8
1.2.5	<i>Physical disability</i>	9
1.2.6	<i>Cancer</i>	9
1.2.7	<i>Serious haemorrhagic events</i>	10
1.2.8	<i>Study Population – gender, age and minorities</i>	11
1.2.9	<i>Conclusion</i>	13
2	STUDY DESIGN.....	13
3	OBJECTIVES	14
4	HYPOTHESIS	14
5	ENDPOINTS.....	14
5.1	Primary Endpoint	14
5.2	Secondary Endpoints.....	15
5.3	Other Measures	15
5.4	Endpoint Ascertainment.....	15
5.5	Endpoint Adjudication Process.....	16
6	STUDY POPULATION	16
6.1	Inclusion criteria.....	16
6.2	Exclusion criteria	17
6.3	General Practitioner (GP) recruitment	18
6.4	Participant identification.....	18
6.5	Participant discontinuation.....	19
6.6	Contingency Plans for Participant Well-being.....	19
6.6.1	<i>Follow up of participants ‘off protocol’</i>	20
6.6.2	<i>Anaemia diagnosed in a study participant</i>	20
6.6.3	<i>Major surgery</i>	20
6.6.4	<i>Major bleed</i>	20
6.6.5	<i>Abdominal discomfort/dyspepsia</i>	21
6.6.6	<i>Commencement of regular non-steroidal mediation (NSAID)</i> ...21	
6.6.7	<i>Development of an indication for aspirin</i>	21
6.6.8	<i>New diagnosis of diabetes</i>	21
6.6.9	<i>Commencement of warfarin or other antiplatelet drugs</i>	21
6.6.10	<i>Commencement of aspirin on own volition</i>	21
7	MEASUREMENTS, CRFs AND ANALYTICAL METHODS.....	22
7.1	Schedule of study visits	22
7.1.1	<i>Lifestyle Profile and Screening visit (Visit 1)</i>	22
7.1.2	<i>Run-in phase (between Visit 1 and Visit 2)</i>	23
7.1.3	<i>Determinations at Eligibility and Assessments visit (Visit 2)</i>	24
7.1.4	<i>Randomisation Procedure</i>	25
7.1.5	<i>Annual Visits</i>	25
7.1.6	<i>Telephone Contact</i>	25
7.1.7	<i>Other Actions</i>	26
7.2	Case Report Forms (CRFs).....	26

7.3	Data Analysis.....	27
7.3.1	<i>Interim Analysis</i>	27
7.3.2	<i>Final Analysis</i>	28
7.4	Dissemination and implementation of results	29
7.4.1	<i>Objectives</i>	29
7.4.2	<i>Approach and Methods</i>	29
8	STUDY MEDICATION AND SUPPLIES	30
8.1	Study treatments	30
8.2	Drug packaging	31
8.3	Administration of study medication	31
8.4	Dispensing and randomisation	31
8.5	Drug storage.....	32
8.6	Drug accountability and dispensing logs.....	32
8.7	Drug disposal.....	33
8.8	Emergency code breaking	33
8.9	Overdosage of trial medication	33
9	CONCOMITANT THERAPY	34
9.1	Oral prescription medications	34
10	SAMPLE SIZE AND POWER CALCULATIONS.....	34
11	ASSESSMENT AND REPORTING OF ADVERSE EVENTS	35
11.1	Serious Adverse Events	35
11.2	Clinically significant bleeding	36
12	ADHERENCE TO ETHICAL, REGULATORY AND ADMINISTRATIVE CONSIDERATIONS	36
12.1	Ethical Considerations	36
12.1.1	<i>General</i>	36
12.1.2	<i>Information for Participants</i>	37
12.1.3	<i>Informed Consent</i>	37
12.2	Regulatory Considerations	37
12.2.1	<i>Financing</i>	37
12.2.2	<i>Trial Registration</i>	38
12.3	Administrative Organisation	38
12.3.1	<i>Individual and Committee Responsibilities</i>	38
12.3.2	<i>Publication Policy</i>	39
12.3.3	<i>Sub-studies</i>	39
13	DATA MANAGEMENT	40
13.1	Data Handling and Record Keeping	40
13.2	Quality Control.....	40
14	REFERENCES	42
	APPENDIX 1. ENDPOINTS AND OTHER MEASURES.....	49
	APPENDIX 2. DETAILS OF SAMPLE SIZE & POWER CALCULATIONS... ..	56
	APPENDIX 3. COMMITTEES	60

1 INTRODUCTION

1.1 Summary

ASPREE is a double-blind, randomised, placebo-controlled primary prevention trial designed to assess whether daily active treatment of 100 mg enteric-coated aspirin will prolong life, free of dementia or significant persistent physical disability, in healthy participants aged 70 years and above. The study will be conducted in general practices across Australia. Participants will be eligible for the trial if they do not have a current clinical indication for (i.e. overt cardiovascular disease) or contraindication (i.e. allergy or increased risk of bleeding) to aspirin, do not have diabetes, dementia, low haemoglobin levels, or have a condition that is likely to be fatal during the 5 years of the trial, and are capable of attending their usual GP's practice and providing informed consent. 18,000 participants will be required to provide 90% power of a true relative risk benefit of 0.90 for the primary endpoint (a composite of all-cause mortality, incident dementia and persistent physical disability) in an intention-to-treat analysis with an average follow-up of 5 years. The trial is supported by the National Heart Foundation, the National Stroke Foundation, Alzheimer's Australia, and the Australian Divisions of General Practice. It has received financial and in kind support from the National Health and Medical Research Council of Australia, the National Heart Foundation of Australia, the Victorian Cancer Agency, CSIRO and Bayer HealthCare.

1.2 Background

Low dose aspirin therapy has been shown to reduce the risk of vascular events in a wide range of primary and secondary care settings, largely in middle-aged people.¹⁻³ There is also some evidence of its potential to reduce the rate of intellectual decline and certain malignancies in older participants.⁴ However part of the benefit of aspirin may be offset by a variety of adverse effects, and in particular, the balance of risks and benefits has not been established in older people. In this context, two recent editorials have identified the need for the ASPREE study to be conducted. Both highlighted the need for prospective data to resolve the current uncertainty regarding the effects of aspirin among the elderly.^{5 6}

1.2.1 Major adverse cardiovascular events

Cardiovascular and cerebrovascular events are the primary cause of death in older adults but they are also major determinants of mental ⁷ and chronic physical disability.⁸ The effect of low-dose aspirin on cardiovascular outcomes has been

tested in both primary- and secondary- prevention randomised clinical trials (RCTs). Meta-analyses of these studies, undertaken by the U.S. Preventive Services Task Force and the Anti-Thrombotic Trialists' Collaboration, have shown that in secondary prevention aspirin therapy reduces the subsequent incidence of cardiovascular death, non-fatal myocardial infarct (MI) and non-fatal stroke by approximately 25%.⁹
¹⁰ The relative risk reduction was similar amongst subgroups based on age, sex, diabetes or underlying disease (i.e. angina, MI, transient ischaemic attack (TIA), stroke or peripheral arterial disease (PAD)).

In primary prevention, the available data has been drawn from six major morbidity/mortality RCTs, whose participants were predominantly middle-aged (in the 50-70 years age group) and at low cardiovascular risk.¹¹⁻¹⁶ Meta-analysis of five of these studies, undertaken primarily in men (>80%), has shown a significant reduction in vascular events, resulting principally from a one third reduction in first MI.¹⁷ There was no significant reduction in stroke, although with the relatively young age of the participants, relatively few cerebrovascular events were recorded.

In 2005 more detailed information became available about the value of aspirin for primary prevention in women. The Women's Health Study (WHS) involved 39,876 apparently healthy women over 45 years of age who were randomised to 100mg aspirin on alternate days and followed for 10 years.¹⁵ The investigators observed a 17% reduction in the risk of stroke (RR 0.83, 95% CI: 0.69-0.99) but no effect on MI (RR 1.02, 95% CI: 0.84-1.25), i.e. the opposite pattern to that seen in men. These findings have since been substantiated by a gender sub-group analysis by Berger¹⁸ who reported that the benefit of aspirin for the primary prevention of major adverse cardiovascular events was driven by acute MI risk reduction in men and thromboembolic stroke risk reduction in women.

The WHS¹⁵ also included a subgroup analysis by age and reported that: *"An interesting finding in our subgroup analyses was that the most consistent benefit of aspirin was observed among women 65 years of age or older. This group of 4097 women composed 10 percent of the study population yet had almost one third of the cardiovascular events. In this group, aspirin use, as compared with placebo use, led to 44 fewer myocardial infarctions, strokes, or deaths from cardiovascular causes (P=0.008) but to 16 more gastrointestinal hemorrhages requiring transfusion (P=0.05), emphasizing, as with any agent, the importance of balancing benefits and risks."*

1.2.2 Cardiovascular benefit versus risk in the elderly

Modelling based on data derived from the primary prevention RCTs suggests that in the middle-aged, at this (low) level of cardiovascular risk, the 'gains and losses' of aspirin are finely balanced. For example, Hayden *et al.* have estimated that for 1000 patients with a 5% cardiovascular risk over 5 years, treatment throughout this period would prevent 6-20 cases of MI, at a cost of 0-2 haemorrhagic strokes and 4 major gastrointestinal events.⁹ For patients with a 1% cardiovascular 5-year risk, aspirin would prevent 1-4 cases of MI but would again cause 0-2 haemorrhagic strokes and 2-4 major bleeds. Because of this lack of clear benefit, aspirin has not been commonly recommended for primary prevention unless the underlying cardiovascular risk is high.^{19 20}

If the proportional benefit and rate of adverse events in older people was similar to those seen in middle-aged people, the modelling might be expected to demonstrate a substantial advantage for aspirin treatment as a result of the higher absolute risk in this group. However, in light of the very limited trial data available for the over 70 age group, and with evidence suggesting a substantially greater rate of adverse events in that age group, such an outcome cannot be assumed. This concern is supported by epidemiological modelling that suggests the benefits of using aspirin routinely for the primary prevention of cardiovascular disease (a reduction of incident MI and ischaemic stroke) in those aged 70 years or more may be offset by increased cases of serious bleeding.²¹ This uncertainty warrants the true balance of risks and benefits for these and other outcomes in older persons to be established by a RCT in sufficient participants to accurately weigh these possibilities and to investigate impacts on other diseases prevalent in older people. In further support for the need for a trial such as ASPREE, a meeting in December 2003 of the FDA Cardiovascular and Renal Drugs Committee voted 11-3 against the expansion of aspirin professional labelling to include moderate-risk individuals for the primary prevention of MI.²²

While clinical trials of routine aspirin use for primary prevention have mainly focused on cardiovascular outcomes, these alone may not be the most appropriate measure of benefit associated with aspirin treatment in the elderly. Prolongation of life free of functional (physical and mental) disability in a healthy ageing population would be the most desirable benefit of a pharmacological strategy focusing on prevention. Underlying causes of death and disability in an ageing population include dementia and cancer, in addition to major cardiovascular events such as stroke, MI and heart failure.

1.2.3 All-cause mortality

In contrast to the secondary prevention studies of aspirin, no primary prevention RCT has yet identified a benefit in terms of all-cause mortality. A meta-analysis by Colin Baigent of the ATT²³ of all six primary prevention trials by age demonstrates that the point estimate of the benefit of aspirin over no aspirin for all-cause mortality is 5%, but with wide confidence intervals. Upon inspection of these trials individually, the aspirin effect ranges from +3% (with no participant over 70 years at baseline¹⁴) to a reduction of 19%.¹⁶ In contrast, the equivalent point estimate for persons over 70 years for major cardiovascular events is 13%. This meta-analysis identifies the futility of an all-cause mortality endpoint alone and supports the treatment effect size and rationale for the choice of mortality plus new onset disability (to which cardiovascular events would make a substantial contribution).

1.2.4 All-cause dementia

There is preliminary, albeit conflicting, evidence to suggest that aspirin may be effective in delaying the onset of vascular dementia, a major cause of cognitive decline in older people.²⁴ Similar evidence is accumulating to suggest that non-steroidal anti-inflammatory drugs (NSAIDs) may also be protective against non-vascular dementia.²⁵⁻²⁷ However, concerns about the long-term cardiovascular safety of selective cyclooxygenase (COX)-2 inhibitors and non-selective NSAIDs support the proposal that aspirin alone amongst this group of drugs has the potential to be used as a preventive agent in this age group.^{28 29} While aspirin's main clinical effect is likely to be via its anti-platelet action (preventing micro-infarcts and stroke), it is possible that it may also produce a dose-dependent anti-inflammatory effect and through this mechanism delay the onset of Alzheimer's disease.^{30 31} For a disease with no known curative or preventive treatment, the public health benefits of delaying onset could be highly cost effective. Brookmeyer *et al.* reported that the potential effects of an intervention (e.g. aspirin) that delayed the onset of Alzheimer's dementia by 2 years would reduce the expected prevalence of the disease in the U.S. by 1.94 million cases after 4 years.³²

Therapeutic measures to prevent the onset of dementia, as opposed to treating the progression of established dementia, may be best targeted towards the early stages of cognitive impairment. Until this time there has been no clinical trial that has adequately assessed aspirin's potential role in delaying the progression of cognitive impairment. A meta-analysis of four observational cohort studies in healthy older people, where cognitive decline was the endpoint, reported no apparent benefit of

NSAID treatment.³³ A more recent report from the WHS cognitive cohort also found no benefit of low dose aspirin (100 mg on alternate days) *versus* placebo in preventing cognitive decline.³⁴ However, the alternate day dosage used, the mean age of 72 years at the first cognitive function measurement (at the younger end of the 'elderly' over 70s) and the insensitivity of the phone-administered tests that were used to assess higher executive functions suggest the need for a further study without these limitations. Indeed, an editorial accompanying the WHS cognitive cohort publication called for 'better quality research into cognitive decline in later life'.³⁵

1.2.5 Physical disability

Aspirin has the potential to decrease the risk of physical function decline by reducing the risk of sub-clinical and clinical stroke, MI and PAD. Subclinical strokes, MIs and PAD as assessed by brain MRI, echo and ECG, and by ankle:brachial index respectively, are all associated with impairment and decline in gait speed, hand grip strength and cognition.³⁶⁻³⁸ In the Cardiovascular Health Study (CHS), the incidence of self-reported difficulty in performing Activities of Daily Living (ADL) in those participants whose MRI revealed the presence of a brain infarct was 8.6 per 100 person-years, compared to 6.7 per 100 person-years in those whose MRI was clear. Gait speed was related to subclinical brain MRI changes, but independent of clinical strokes over the time period.³⁸

1.2.6 Cancer

The possibility that aspirin may have a role in the prevention of cancer has been raised by a number of clinical trials and observational studies. In 2005, a systematic review of data from 91 observational studies showed a statistically significant exponential decline in risk with increasing NSAID dose (primarily aspirin or ibuprofen) for 7 of 10 malignancies.³⁹ Daily intake of NSAIDs (325 mg aspirin or 200 mg ibuprofen) was associated with risk reductions of 63% for colon cancer, 39% for breast, 36% for lung and 39% for prostate cancer. These effects became evident after five or more years of use and increased with increasing duration of therapy. More recently a 10 year follow-up of participants in the Iowa Women's Health Study (IWHS) found that regular aspirin use was associated with a 16% reduction in incident cancers from any site, but that other NSAIDs caused no reduction.⁴⁰ By contrast the WHS, a randomized placebo-controlled trial, showed no overall benefit for very low-dose aspirin (100mg on alternate days) over placebo for newly diagnosed invasive cancer at any site.⁴¹

Evidence of aspirin's action is particularly strong for colorectal cancer, the third most frequently occurring cancer in Caucasian men and women.⁴² The risk of this malignancy increases rapidly with age, with the highest incidence found in people aged 85 and over.^{42 43} Two RCTs have demonstrated that aspirin can reduce the incidence of new adenoma development in individuals with a history of cancer or previous adenomas.^{44 45} Investigators from the Nurses Health Study (NHS) reported a relative risk reduction in colorectal cancer incidence of 0.77 (95% CI: 0.67-0.88) for women classified as "regular" aspirin users ($\geq 2 \times 325$ mg tablets / week),⁴⁶ which is within the dosage range of aspirin use for cardiovascular disease prevention.

More recently Chan and colleagues⁴⁷ reported that regular aspirin use was associated with a 36% decrease in the incidence of colorectal cancer amongst 130,000 health professionals followed in longitudinal cohort studies in the U.S. This effect was seen only amongst the 67% of colorectal malignancies that over-expressed the COX-2 enzyme. Flossman and Rothwell found in a recent meta-analysis of two U.K. RCTs that regular use of aspirin was associated with a 26% lower risk of colorectal cancer incidence, but the effect required a combination of high dose and a prolonged duration of treatment (5 years) and follow-up (10 years) to become statistically significant.⁴⁸ This provides a possible explanation as to why two U.S. trials (the Physician's Health Study and the WHS) failed to identify a similar effect.^{41 49}

The U.S. Preventive Services Task Force recently concluded that on present evidence, the harms of aspirin use outweigh the benefits for the prevention of colorectal cancer.^{41 43 46 49} However the overall trend in data suggests that a RCT in older participants is needed to resolve the question of whether regular low-dose aspirin use is preventive for colorectal malignancy in those aged 70 and above. In this context, a sub-group analysis of women aged 65 - 74 years within the NHS cohort revealed a 22% decrease in the relative risk of (all) cancer mortality with regular aspirin use.⁵⁰

1.2.7 Serious haemorrhagic events

The potential risks of aspirin therapy may be greater in older people compared with the more extensively studied middle-aged (Section 1.2.2). The recent WHS reported significant increased gastrointestinal bleeding events with aspirin in the participant population overall and, of note, in the subgroup aged 65 years or more.¹⁵ Cohort data suggests a higher absolute risk of gastrointestinal haemorrhage amongst older participants, and if so it is likely that lesser degrees of bleeding will also be more

common (Figure 1).⁵¹ This latter concern was demonstrated in both PACE and ASPREE pilot studies, where there was an average haemoglobin reduction of 0.2 gm% in those receiving low-dose aspirin compared to placebo. ASPREE will provide an opportunity to investigate whether such findings are limited to the first year of treatment or are an ongoing trend.

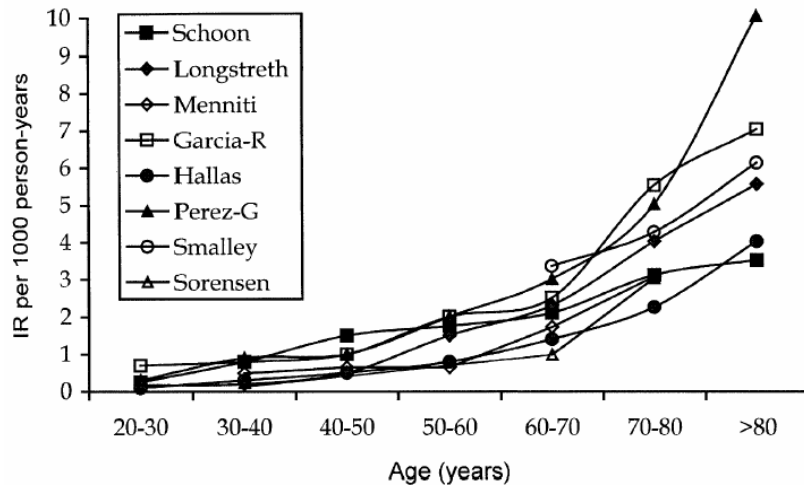


Figure 1. Incident rates of serious upper gastrointestinal complications per thousand person-years by age. Reproduced from Hernandez-Diaz and Garcia Rodriguez.⁵¹

There is also residual uncertainty about the extent of the risk of intracerebral haemorrhage in older people with low-dose aspirin therapy.^{52 53} The risk of intracerebral haemorrhage generally is substantially higher in older persons; the impact of this risk may therefore be magnified with regular low-dose aspirin intake.⁵⁴

Distinction between ischaemic stroke and haemorrhagic stroke can not be accomplished reliably without CT scanning. In Australia such imaging is undertaken in virtually all cases of suspected stroke and results will be sought for presentation to the Endpoint Adjudication Committee (EAC). This will allow ischaemic and haemorrhagic stroke to be determined separately during the course of ASPREE.

1.2.8 Study Population – gender, age and minorities

The Australian elderly population, like the U.S., is a multicultural society with a residual indigenous population overwhelmed by historic and continuing immigration (Table 1).

Age (years)	Australia	USA
65-74	32	14.6
75-84	28	8.0
85+	29	3.2

Table 1. Percentage of the elderly foreign-born in Australia and the USA. Sources US Census 2000 and Australian Demographic Statistics, December Quarter 1999 (ABS Catalogue number 3101.0)].

Life expectancy data from the WHO suggests similar life expectancy profiles amongst the older population of both nations (Figure 2). Comparative data for age-standardised death rates also suggests similar prevalence of all-cause mortality, cardiovascular disease (CVD) and cancer (Table 2).

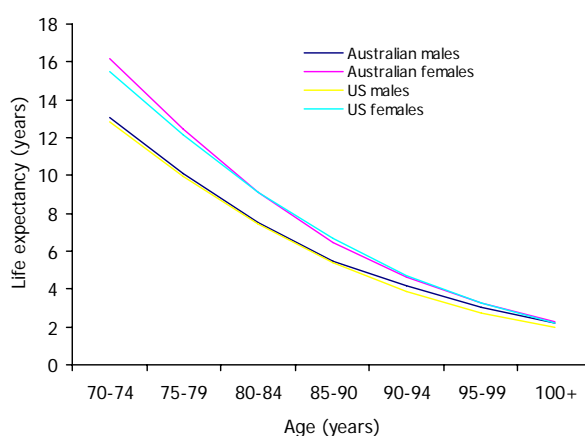


Figure 2. A comparison of Australian and US life tables 2000 (<http://www.who.int/country/en/>)

Condition	U.S. males (2002)		U.S. females (2002)		Aus males (2003)		Aus females (2003)	
	65-84	85+	65-84	85+	65-84	85+	65-84	85+
All cause	3832	16255	3312	14210	3487	15937	2291	13259
CVD*	1759	7142	1180	6785	980	5746	655	5280
Malignancies	1152	2491	848	1391	1238	2893	715	1535

Table 2. Death rates per 100,000 population by age for all-cause mortality, major cardiovascular disease (CVD; heart and cerebrovascular) and cancer. Sources: 2002 US data⁵⁵ and 2003 Australian data⁵⁶. * CVD rates for US males and females are higher than that identified in Australia. This is primarily due to the differences in definitions of CVD used in these surveys and ethnic differences in populations where the Australian population is primarily Caucasian.

1.2.9 Conclusion

Low-dose enteric-coated aspirin is potentially one of the most effective preventive agents for use in older participants. It has the potential to extend the duration of the healthy active life of older people by delaying the onset of CVD, stroke and possibly dementia. These are the most common causes of physical disability and hospitalisation in the senior Australian population, which is growing rapidly. If proven effective, the low cost of aspirin therapy would make it an affordable preventive agent for older populations in all countries. On the other hand there is a possibility that the benefits may be largely offset by increased risks of serious bleeding and a progressive decline in haemoglobin levels.⁵⁷ No study to date has adequately examined the balance of risks and benefits of aspirin therapy in the elderly, hence the need to conduct a RCT in a sufficient number of participants to accurately weigh these possibilities.

2 STUDY DESIGN

ASPREE is a randomised, double blind, placebo-controlled trial. Participants will be randomised remotely by centralised telephone IVRS (Interactive Voice Recognition System) based at the ASPREE Data Management Centre (DMC) or via the ASPREE Data Management Centre web portal. For both systems, password protected access is required for study personnel. According to a computer-generated randomisation schedule, participants will be allocated to 100 mg enteric coated aspirin or placebo in a ratio of 1:1. Randomisation will be stratified for general practice and for age (70-79 or ≥ 80 years).

During an initial 4 week run-in phase participants will take placebo for compliance checking. Bayer HealthCare will supply active drug and matching placebo. Participants will be instructed to take their aspirin or placebo half an hour prior to any morning medication to minimise drug interactions.

Pre-screening on practice database	Lifestyle Profile & Screening (Visit 1)	Run-in phase & GP visit	Assessments & Eligibility (Visit 2)	Annual Visit (1)	Annual Visit (2)	Annual Visit (3)	Annual Visit (4)	Annual Visit (5)
	↓	↓	↓	↓	↓	↓	↓	↓
Time	-4 weeks		0	Year 1	Year 2	Year 3	Year 4	Year 5
6 monthly telephone contact between randomisation and annual reviews								

Table 3. Timeline for ASPREE.

3 OBJECTIVES

Primary Objective

The primary objective is to determine whether low-dose aspirin prolongs life free of dementia or significant, persistent physical disability in the healthy elderly.

Secondary Objectives

Secondary objectives relate to the effects of low-dose aspirin on the key outcome areas of death, cardiovascular disease, dementia and cognitive decline, cancer, physical disability and major bleeding episodes – see Section 5.2.

Other Measures

Measures in addition to those included in the primary and secondary objectives will be examined. These include measures such as haemoglobin levels, tests of mental and physical function and hospitalisations – see Section 5.3.

4 HYPOTHESIS

Null hypothesis: Daily 100 mg enteric-coated aspirin will have no benefit over placebo in reducing numbers of deaths, new onset dementia or physical disability in healthy participants aged 70 years and over.

Alternative hypothesis: Daily 100 mg enteric-coated aspirin will cause a 10% reduction in numbers of deaths, new onset dementia or physical disability in healthy participants aged 70 years and over.

5 ENDPOINTS

Clinical and ancillary evidence must be supplied by the investigator to support all diagnoses. Major adverse cardiovascular, but not dementia, endpoints lead to withdrawal from “on randomised treatment” but not from intention-to-treat follow-up.

Detailed definitions of the endpoints and other measures are provided in Appendix 1: Endpoints and Other Measures.

5.1 Primary Endpoint

The primary endpoint is death from any cause or incident dementia or persistent physical disability. Dementia will be defined from a clinical diagnosis based on DSM-IV criteria. Persistent physical disability will be defined as a progression by at least 2 intervals on a 5-point scale of, or a loss of ability to perform independently, any one

of the 6 Katz Activities of Daily Living (ADLs).⁵⁸

5.2 Secondary Endpoints

Secondary endpoints include:

- All-cause mortality
- Fatal and non fatal cardiovascular events including a) coronary heart disease death, b) non-fatal MI, c) fatal and non-fatal stroke and d) any hospitalisation for heart failure
- Fatal and non-fatal cancer, excluding non-melanomatous skin cancer
- Dementia
- Cognitive decline (assessed using the Modified Min-Mental State Examination or 3MS⁵⁹)
- Physical disability
- Major haemorrhagic events

These secondary endpoints will also help explain any differences between treatment groups in the primary endpoint.

5.3 Other Measures

These outcomes include:

- Additional cognitive function measures (Digit Symbol Substitution Test or DSST⁶⁰, Hopkins Verbal Learning Test-Revised or HVLTR⁶¹, Single Letter Fluency Test or SLFT⁶²)
- Depression (Center for Epidemiologic Studies – Depression or CES-D⁶³)
- Physical function measures: performance-based (including gait speed and hand grip tests) and self-reported (LIFE questionnaire⁶⁴)
- Quality of life (Short Form – 12 or SF-12⁶⁵)
- Haemoglobin levels
- Hospitalisation (for reasons other than primary or secondary endpoints)

5.4 Endpoint Ascertainment

At each annual visit and telephone contact, the participant will be questioned as to the occurrence of any of the study endpoints over the previous 6 months. Notification of a potential study endpoint will trigger the collection of information for endpoint confirmation and adjudication by the Endpoint Adjudication Committee (EAC). All such events will be recorded in source documents and in the appropriate section of the Case Report Form (CRF). Confirmation of endpoints will be ascertained by collecting information from the following sources:

- The usual treating GP or practice-held medical record.
- Letter/fax/email contact with other treating specialist physicians or secondary/tertiary medical care centres for evidence regarding possible endpoints.
- CRFs containing standardised questionnaires for the assessment of cognitive function, physical function and quality of life.
- Hospital records/discharge summaries, pathology reports.
- Death Certification: The National Death Index, housed by the Australian Institute of Health and Welfare, will be routinely sourced for notification of death not identified through the above processes.

5.5 Endpoint Adjudication Process

Each study endpoint will be notified to the ASPREE Data Management Centre (DMC) using the specific *Clinical Event Notification* CRF. In addition, all supporting information derived from medical records, hospital discharge summaries and medical investigation reports will be collected, copied, attached to the *Clinical Event Notification* CRF and sent to the ASPREE DMC. Original data will be retained at each study site as source data.

On receipt at the ASPREE DMC, all endpoint information will be collated. An ASPREE Data Centre Manager will be responsible for the presentation of study endpoint documentation to the EAC on a pre-determined schedule. Additional information requested by the EAC will be communicated to the site via the Data Centre Manager. The EAC will meet via videoconference on a quarterly basis to discuss: a) the quality of endpoint information being received, b) the adjudication process and any difficulties or operational concerns, and c) the rate of endpoint accumulation. The EAC consists of five individuals chosen by the ASPREE Steering Committee (see Appendix 3: Committees). Case material will be reviewed by at least two members and if there is disagreement a third member will be asked to adjudicate.

6 STUDY POPULATION

6.1 Inclusion criteria

- Men and women 70 years of age and over
- Non-institutionalised

- Willing and able to provide informed consent, and willing to accept the study requirements
- Physically capable of regularly attending his/her family physician.
- Without major cardiovascular disease, dementia or other exclusion criteria, as listed below.

6.2 Exclusion criteria

- A history of a diagnosed cardiovascular event defined as MI, heart failure, peripheral arterial disease, angina pectoris, stroke, transient ischemic attack, >50% carotid stenosis or previous carotid endarterectomy or stenting, coronary artery angioplasty or stenting, coronary artery bypass grafting, or abdominal aortic aneurysm.
- A serious intercurrent illness likely to cause death within the next 5 years, such as terminal cancer or obstructive airways disease.
- A current or recurrent condition with a high risk of major bleeding, e.g. cerebral aneurysm or cerebral AV malformation, any bleeding diathesis, gastrointestinal malignancy, recent peptic ulcer, liver disease, oesophageal varicosities, uremia, aortic aneurysm or any other condition known to be associated with a high risk of serious bleeding.
- Anaemia, i.e. haemoglobin level below the normal value for the gender of the participant (males: 13g/L, females: 11.5 g/L).

(Note: Haemoglobin levels within the normal range in a participant taking therapy for anaemia will not be an exclusion criterion).

- Absolute contraindication or allergy to aspirin.
- Current participation in a clinical trial.
- Current continuous use of aspirin or other anti-platelet drug or anticoagulant. Participants with previous use may enter the trial, provided they have been off the medication for 3 months. (Concurrent use of a NSAID is not an exclusion criterion but subjects are requested to take their trial medication 30 minutes prior to other medications.)
- A systolic blood pressure ≥ 180 mmHg and or a diastolic blood pressure ≥ 105 mmHg

- A history of a clinical diagnosis of diabetes (glucose ≥ 7.0 mmol/L (fasting) or ≥ 11.1 mmol/L (non fasting))
- A history of dementia or a Modified Mini-Mental State Examination (3MS) score ≤ 77 as measured at Visit 1: *Lifestyle Profile and Screening*.
- An inability to perform independently, or more than 'A little difficulty' reported in performing, any one of the 6 Katz ADLs, as determined at Visit 1: *Lifestyle Profile and Screening using the LIFE Disability Questionnaire*.
- Pill-taking compliance outside the range of 80-120% during the placebo run-in phase.

6.3 General Practitioner (GP) recruitment

This study will utilise the unique resource established for the ANBP2 trialist collaboration for the conduct of large-scale trials in family practice.⁶⁶⁻⁶⁸ That study involved the recruitment and follow-up of over 6000 participants in a family practice setting.⁶⁹ The recruiting base involves collaborating Departments of General Practice in universities across Australia which identify and recruit Regional Medical Officers (RMOs) and Research Nurses (RNs). The RMOs then approach individual family GPs to support the project and explain the rationale and implications for the GP's practice. GPs indicating a willingness to receive more information will be sent an information package further describing the study and a site visit will be made to discuss the study with the RMO or a senior study nurse. For group practices, each GP will be approached individually by an initial telephone call, but the site visit will be arranged with all interested GPs in the practice. A *study site evaluation checklist* will be completed to ensure that the study site has the required facilities and resources to participate satisfactorily in the ASPREE study. Following the site visit and confirmation of participation, the *GP Investigator Registration form* and *Practice Registration form* are completed, and the clinic becomes a registered ASPREE clinical practice.

6.4 Participant identification

Patient databases from each registered practice will be reviewed for participant inclusion and exclusion criteria by RNs or research staff. Family GPs will be given assistance to comply with the requirements of the privacy legislation. RNs will ensure appropriate signage is displayed in waiting rooms communicating the fact that the practice is participating in research and that patients can opt out of providing data for the study. Study nurses may also sign staff confidentiality agreements to become

'agents of the practice'. Following the generation of a list of potential study participants, the GPs then review the database printout of the search results to ensure that invitees meet inclusion and exclusion criteria. Each GP-approved individual who appears to meet these criteria is sent a letter from their usual primary care GP, inviting them to consider participation in the trial. The letter advises those who are interested to call a toll free 1800 number to discuss their participation in the study. At this initial telephone contact, willingness of the person to participate will be ascertained and information relating to exclusion criteria will be sought and recorded on the *Phone Screening form*. For those patients willing to participate and in whom there are no obvious exclusion criteria, an appointment will be made with the local RN to attend the practice premises for the screening visit and subsequent enrollment in the study (Visit 1).

6.5 Participant discontinuation

As the aim of the study is to assess ultimate outcome following randomisation to one of the treatment arms, attending GPs will be strongly encouraged to continue participants on their randomised treatment. 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, or attending GP's decision to withdraw the participant. If a participant withdraws from the study altogether (i.e. from taking study medication and from attending annual visits) or is removed from the study for any reason, then the *Subject Exit* CRF will be completed.

The occurrence of a non-fatal endpoint is not necessarily a condition for withdrawal – the participant will be requested to continue to attend routine annual visits for the ascertainment of further endpoints, and may be asked to continue taking their study medication (eg. if the endpoint that occurred is not a major adverse cardiovascular event and does not provide an indication to commence – or cease – aspirin therapy).

The first non-fatal endpoint experienced 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.

6.6 Contingency Plans for Participant Well-being

Participants will be advised to seek advice from their usual treating GP for any medical condition arising during the course of the study. Treating GPs will be

provided with information about the study and suggestions about clinical approaches to optimise clinical management and maintain the subject's participation in the study (wherever possible).

6.6.1 Follow up of participants 'off protocol'

"Off protocol" is defined as: study participants who commence aspirin therapy or cease trial medications on clinical grounds (6.6.2-6.6.10) or because of a lack of preparedness to continue in the study.

Regardless of the decision to continue with the study medication, the participant will be asked to attend all scheduled follow-up visits. Those who are unwilling to do this will be asked for approval to continue follow-up through surveillance of their clinical records and through linkage to electronic morbidity and mortality databases. All participants will be asked to provide approval for access to this information as part of the study enrollment procedures. In all cases where a participant ceases taking their study medication, the reason for discontinuation, the date of discontinuation and date of the last dose of study medication, should be recorded.

6.6.2 Anaemia diagnosed in a study participant

Haemoglobin results will be provided to the usual treating GP on an annual basis as part of the annual follow-up report for the participant. The treating GP will be advised to follow their routine clinical practice for the management of patients with anaemia. When the cause of the anaemia is determined to be blood loss and when the cause of blood loss is identified (e.g. a bleeding colonic polyp), encouragement will be given to recommence the trial drug once the underlying cause is treated. Similarly, GPs may choose to advise participants to recommence their study medication if the anaemia has responded to therapy such as iron replacement.

6.6.3 Major surgery

Participants will be advised to contact the RN when any surgery is planned. Their GP will be advised to treat the participant as if they are taking aspirin and that the participant may temporarily cease the trial drug if they consider it advisable. No unblinding will occur. Participants will be encouraged to recommence study medication at a time determined by the participant's surgeon in consultation with their usual treating physician.

6.6.4 Major bleed

Participants will be advised to cease randomised study medication on diagnosis of a

non-traumatic major haemorrhage, e.g. a bleeding peptic ulcer. Such an occurrence will typically represent a reason to cease randomised treatment.

6.6.5 Abdominal discomfort/dyspepsia

Participants will be advised to discuss abdominal discomfort / dyspepsia with their usual treating GP. Both physician and participant will be advised that the ASPREE pilot studies suggest that only 20% of such symptoms are likely to be due to the active trial drug. If symptoms are persistent the recommendation will be to cease the study medication for a trial period and then re-challenge. If symptoms recur then the GP may add other medication (e.g. a proton pump inhibitor) or cease the trial drug.

6.6.6 Commencement of regular non-steroidal mediation (NSAID)

Participants will be advised to avoid continuous NSAID use. If they take NSAIDs they will be advised to take them at least half an hour after taking trial medication to minimise interaction. Details of all NSAID use will be recorded.

6.6.7 Development of an indication for aspirin

Participants who develop a recognised clinical indication for continuous use of aspirin may commence routine aspirin.

6.6.8 New diagnosis of diabetes

All participants will be advised to discuss a new diagnosis of diabetes with their usual treating GP. The decision to cease the study medication and commence active aspirin will be made by the GP in consultation with their patient.

6.6.9 Commencement of warfarin or other antiplatelet drugs

Should a clinical indication arise for the use of warfarin or other antiplatelet drugs, it will be the responsibility of the participant's usual treating GP to advise whether or not the participant should continue with study medication.

6.6.10 Commencement of aspirin on own volition

All participants sign a plain language information and consent form at study entry that states:

“For the duration of the study you should not take any medication containing aspirin. If you have any questions in this regard please contact the study nurse.”

However it also states:

“Participation in the study is voluntary. You can choose not to participate in part

or all of the study and can withdraw at any stage without being penalised or disadvantaged in any way.....Your decision whether or not to participate is entirely voluntary and will not prejudice your future relations with your GP.”

Hence, although it will be discouraged, participants are entitled to commence aspirin if they so choose.

7 MEASUREMENTS, CRFs AND ANALYTICAL METHODS

7.1 Schedule of study visits

The trial is primarily designed to assess mortality and morbidity although other measures will be determined. The ASPREE Measurement and Study Activity schedule for each of the study visits is summarised in Table 4.

7.1.1 Lifestyle Profile and Screening visit (Visit 1)

Measurements and data will be collected by the RN after the participant has provided informed consent to participate in the study. Each study participant will be assigned a unique id number, which will be used throughout the study. The information to be collected at this visit (and thereafter at some or all Annual Visits* - see Table 4) includes:

- a) Basic demographic and lifestyle factors including living situation*, ethnicity and language, personal medical history*, smoking history*, alcohol use*, medication history* and level of education.
- b) Family history of acute MI, stroke or dementia – identified by participant and from medical case notes.
- c) Blood pressure*: measured in the seated position following 5 minutes of rest using an oscillimetric device. The average of the last two of three measurements taken 30 seconds apart will be recorded.
- d) Cognitive function*: assessed using the Modified Mini-Mental State Examination (3MS) score ⁵⁹ and the Center for Epidemiologic Studies – Depression (CES-D) ⁶³ questionnaires. The 3MS will be implemented as part of the screening of participants (where the score will be used to determine eligibility for the study) and will be administered again at years 1, 3 and 5.

The CES-D is a self-administered questionnaire used to screen for depression. It will be used in association with the 3MS, as depression is a confounder for cognitive function ascertainment.

- e) Physical disability*: assessed by the participant's self-reported ability to perform the 6 Katz Activities of Daily Living (ADLs), which form a component of the Lifestyle Interventions and Independence for Elders (LIFE) Disability questionnaire.⁶⁴
- f) A referral to a local Pathology Provider for a fasting blood sample collection* (~12 ml), for the measurement of total cholesterol, LDL-C, HDL-C, triglycerides, glucose, creatinine and haemoglobin.
- g) Placebo medication for the run-in phase of 4 weeks will be dispensed to enable subsequent determination of medication compliance during this period.
- h) Review of inclusion / exclusion criteria.

Measurement / Activity	Lifestyle Profile & Screening (Visit 1)	Assessments & Eligibility (Visit 2)	Annual Visit (1 yr)	Annual Visit (2yr)	Annual Visit (3yr)	Annual Visit (4yr)	Annual Visit (5yr)
Review inclusion/ exclusion criteria	X	X					
Obtain informed consent	X						
Dispense medication	X (placebo only)	X	X	X	X	X	
Assess medication compliance		X	X	X	X	X	X
Blood pressure ^a , height ^b , weight ^b & abdominal circumference ^b	X ^a	X ^b	X	X	X	X	X
Demographics, family & personal history, medications, lifestyle factors	X		X	X	X	X	X
Laboratory testing - Fasting blood: total cholesterol, HDL, LDL, triglyceride, glucose, creatinine & hemoglobin	X		X	X	X	X	X
Quality of life - SF-12	X		X	X	X	X	X
Assess cognitive function - 3MS ^a , CES-D ^a , DSST ^b , HVLT-R ^b & SLFT ^b	X ^a	X ^b	X		X		X
Assess physical disability - LIFE Disability Questionnaire	X		X	X	X	X	X
Assess physical function - Walk test and grip strength		X		X		X	X
Clinical event reporting - Questionnaire & medical record review		X	X	X	X	X	X

Table 4. ASPREE Measurement and Study Activity Schedule.

7.1.2 Run-in phase (between Visit 1 and Visit 2)

During the one month run-in phase between Visit 1 and Visit 2, while taking placebo medication, the participant is also required to:

- a) Provide a fasting blood sample at a local Pathology Provider. Laboratory results will then be sent to the relevant ASPREE study site – these will be used to satisfy inclusion and exclusion criteria.

- b) Consult his / her GP, whereupon the GP will complete a physical examination to determine the participant's suitability for randomisation in the trial.

7.1.3 Determinations at Eligibility and Assessments visit (Visit 2)

At the end of the 4 week run-in phase, the 'Assessments & Eligibility visit' (Visit 2) will be undertaken at the participant's family GP's practice, or at a regional ASPREE Study Centre. At this visit (and, unless stated otherwise, at every Annual Visit) the following measurements and study activities will be conducted:

- a) Medical co-morbidity – medical record review / participant self-reporting.
- b) Short Form (SF) -12 score ⁶⁵ – self-administered questionnaire for quality of life.
- c) Additional cognitive function tests: the Digit-Symbol Substitution Test (DSST) ⁶⁰, the Hopkins Verbal Learning Test (HVLT-R) ⁶¹ and the Single Letter Fluency Test (SLFT; from the Controlled Oral Word Association Test (COWAT) ⁶²). These tests will then be performed in years 1, 3 and 5 (close-out), in conjunction with the 3MS (and CES-D, for confounding of depression) – see Table 4.
- d) Height – measured, without shoes standing against a wall using a calibrated stadiometer. Measured again at Year 5 (close-out).
- e) Weight and waist circumference – measured following the removal of excess clothing and with calibrated scales. Waist circumference will be measured according to the NHANES III Protocol (<http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=obesity.box.236>).
- f) Physical function testing – timed gait speed test for 3m (8ft) ⁷⁰ and hand grip strength measured on a grip strength dynamometer.⁷¹ Physical function testing will be performed in years 2, 4 and 5 (close-out) – see Table 4.
- g) Concomitant medications, indication and year commenced – participant self-reporting, medical record review and family physician report.
- h) Medication compliance – the number of tablets returned at this visit to the number expected with 100% compliance. Adequate adherence to placebo during the run-in period is an inclusion criterion for the study and is defined as pill count greater than 80% and less than 120% of those required to be taken during this phase.
- i) Information on relevant current major illnesses.

Participants' contact details will also be confirmed, to ensure the dispensing of study medication to the correct mailing address.

7.1.4 Randomisation Procedure

Following the completion of data collection at Visit 2, and if all inclusion criteria are satisfied, participants will be randomised to a treatment arm via the telephone or the internet. Telephone randomisation will be via a toll free 1800 IVRS (Interactive Voice Response System) established at the ASPREE DMC. For large clinical centers, randomization will be achieved via the ASPREE DMC web portal. For both systems, password protected access is required for study personnel. Staff will be required to enter their unique ASPREE Identification number along with the following key information: study site number, ASPREE participant identification number, age and gender of participant, and confirmation of inclusion / exclusion criteria.

Computer-generated medication numbers will be provided to trial sites through the IVRS or the web portal. The randomisation list will be generated by an independent statistician. This arrangement will ensure that the randomisation code remains inaccessible to all study staff and senior investigators. The randomisation list will be generated using the STATA “ralloc” procedure with randomisation stratified for site and age (<80 yrs and ≥80 yrs). Following the completion of the randomisation process by the RN / research assistant, a study medication number will be provided. All staff remain blinded to treatment allocation through the randomisation procedure. The RN or research assistant is required to immediately confirm the study medication number through the IVRS / web portal system. The subsequent distribution of drug is detailed in Section 8. Records of all participants who have undergone screening and randomisation will be made by completing the appropriate forms (*Master Subject Log, Screening & Enrollment Log*).

7.1.5 Annual Visits

At Annual Visits, measurements undertaken at baseline (refer to sections 7.1.1 and 7.1.3) will be repeated using identical protocols, in accordance with the ASPREE Measurements and Study Activity Schedule (Table 4). Additionally, Serious Adverse Events (SAEs) and potential clinical endpoints will be collected by participant report. Following notification, clinical information relating to the SAE or endpoint will be sourced through: a) medical record review and b) hospital records and discharge summaries. Specific procedures for endpoint ascertainment and adjudication have been outlined previously in sections 5.4 and 5.5, respectively, of this protocol.

7.1.6 Telephone Contact

Each participant will be contacted by telephone, initially if receipt of trial drug has not been registered, and where possible six monthly after baseline and each Annual Visit

in order to encourage compliance to treatment allocation, and to identify new onset of SAEs or potential study endpoints.

To ensure any two point loss of Katz ADL identified at an Annual Visit is sustained and not transient, the loss will be confirmed at the subsequent telephone contact at six months.

7.1.7 Other Actions

If the participant does not proceed to randomisation, then the reason for non-randomisation is to be documented and collected on the designated CRF.

Any test measurement result that is outside the normal range will trigger a notification to the participant's GP. Such measurements include: 3MS, CES-D, haemoglobin and glucose levels, blood pressure levels (for details, see Appendix 1: Endpoints and Other Measures).

7.2 Case Report Forms (CRFs)

CRFs are used to record clinical study data and are an integral part of the 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 the error on a free space. All corrections must be initialed and dated.

CRFs will be provided for each participating family practice. At the end of a participant visit, the RN will either fax the completed CRFs to the ASPREE Data Management Centre (DMC) for data entry or transfer the data directly onto electronic CRFs that are accessible via the ASPREE website, and retain the original hard-copy CRFs and other source documents, stored in the participant's file.

At the end of the 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. Appropriately coded identification (GP-, Practice- and Subject- Identification Numbers) and participant initials must be used. The RN / family GP investigator must keep a separate confidential record of full patient details (*Subject Identification Log*) to permit identification of all participants enrolled in a clinical study to ensure case follow-up if required.

7.3 Data Analysis

The trial will be analysed by statisticians based at the ASPREE DMC, Department of Epidemiology and Preventive Medicine, Monash University.

7.3.1 Interim analysis

Event rates are not expected to be uniform during the trial; they are expected to increase over time as participants age, and as more participants are enrolled. Hence we do not expect half the expected number of events ($n/2$) to accrue until over half way through the study duration. Although there will be some lag-time for the processing and adjudication of events, this usually will occur within three months. Overall, the opportunity to undertake interim analyses on the basis of accrued number of events is limited to the latter stages of the trial. Based on this consideration a single interim analysis is pre-specified.

The primary outcome will be monitored by the Data Safety and Monitoring Board (DSMB; see Appendix 3) using a Haybittle-Peto stopping rule at this interim analysis when half of the expected number of events has accrued.⁷² The p-value boundary for comparison of treatment groups at this interim analysis will be 0.01. All-cause mortality will be continuously monitored using sequential likelihood ratio tests to compare treatment groups with standard boundaries of 9.5 and 0.055 (defined using alpha and beta errors of 5% and 10%, respectively).⁷² The DSMB will be responsible for reviewing these interim analyses and providing a recommendation to the Steering Committee.

The accrual of events will also be monitored. If event rates are higher than expected, then either the expected rates are underestimates or there is a harmful effect of aspirin. In either case the planned interim analysis at $n/2$ (adjudicated) events is appropriate to guide monitoring of the study. If event rates are lower than expected, then either expected rates are overestimates or there is a stronger beneficial effect of aspirin than anticipated. In the second case the planned interim analysis at $n/2$ (adjudicated) events is appropriate to guide monitoring of the study. However if observed event rates are lower than expected, while this will affect both study groups equally and therefore not affect the scientific validity of the trial, its feasibility will be affected since follow-up of participants will be needed. In this case a decision will need to be made by the DSMB regarding the utility of continuing the study. To aid this decision-making an additional interim analysis of the primary outcome will be performed after $n/4$ events if this has not occurred within 3 years of the time when the final participant was enrolled into the study. The Haybittle-Peto p-value boundary at this interim analysis is 0.01. Conditional power calculations will also be performed on

the basis of anticipated treatment benefit to assist deliberations by the DSMB concerning the study. If the study continues, the planned interim analysis at n/2 events will proceed and be accompanied by conditional power calculations.

7.3.2 Final analysis

All primary and secondary outcomes will be in the form of time-to-event data and rate ratios will be calculated using univariate Cox proportional hazards regression to directly compare event rates between treatment groups. In analyses of secondary endpoints, death due to causes other than those specified by the endpoint and loss to follow-up (see below) will be considered as censoring events. Given the large sample size, we anticipate randomisation will adequately balance baseline characteristics of participants in the two treatment groups. If necessary, a secondary set of analyses will be performed to adjust for baseline characteristics that are found to be imbalanced between groups to the extent of a 0.25 standard deviation difference in means (quantitative measures) or an odds ratio of 1.5 (binary measures). These analyses will be conducted using multivariate Cox proportional hazards regression models.

The primary and secondary endpoints will be analyzed according to intention-to-treat principles, i.e. according to the group to which participants were randomised and without reference to their actual compliance with assigned treatment. No statistical adjustment will be made for the multiple secondary endpoints in their analysis^{73 74} but the reporting of all secondary endpoint analyses will make clear whether the primary endpoint was statistically significant⁷⁴ and will state the number of secondary endpoints proposed *a priori* in the study protocol.⁷³

Pre-specified sub-group analyses will be undertaken using appropriate interaction terms in Cox proportional hazards regression models. The p-values for these interaction terms will be used to test for heterogeneity of treatment effect of aspirin between sub-groups.

In the survival analyses, loss to follow-up will be considered a censoring event. This equates to an assumption that data is missing at random given the participant's treatment group and the timing of their loss to follow-up. The adequacy of this assumption will be checked by using logistic regression to compare baseline characteristics between participants who are lost to follow-up and participants who complete the study. Any characteristics found to be predictive of loss to follow-up will be adjusted for in a secondary set of analyses of study endpoints. In these analyses the assumption regarding missing data will therefore be missing at random given treatment group, time to censoring and baseline characteristics predictive of loss to

follow-up.⁷⁵

Baseline characteristics that are quantitative measurements will be checked across the range of measures as part of data cleaning prior to statistical analysis. This will ensure that perceived outliers are not data entry errors. A genuine outlier will be defined as a measurement that is greater than three standard deviations from the mean, on a log-transformed scale if measurements are approximately log-normally distributed on their original scale. Regression diagnostics will be used to assess the influence of genuine outliers on treatment comparisons in analyses that include a quantitative baseline characteristic. Where outliers are found to exert such an influence, a secondary analysis will be performed with the outliers removed and the results of the two analyses will be reported.

7.4 Dissemination and implementation of results

7.4.1 Objectives:

Implementation of a theoretically based dissemination intervention, similar to that of the Antihypertensive and Lipid-Lowering Heart Attack Trial (ALLHAT).

- a) To increase awareness of the ASPREE trial by disseminating results via repetitive messages through scientific and professional channels.
- b) To provide GPs, GPs' assistants or nurse practitioners with cues to action via distribution of office posters, prescription cards, and other educational materials.

7.4.2 Approach and methods:

The following represents various strategies to disseminate 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 (in addition to providing a means by which authorised ASPREE personnel can send data, using electronic CRFs). The web site will consist of published journal articles, newsletters, presentations, a frequently asked questions (FAQs) section, links to other 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. Select slide sets, i.e. major outcomes, will be available in other languages, including Spanish. Slides will be accessible via the ASPREE web site. A set of slides will also be developed for presentation to consumers.

- *Formulary systems approach.* Similar to the ALLHAT dissemination, 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 GP practice posters, reference cards, and consumer brochures will be effective tools for disseminating study findings and recommendations. Office posters and reference cards will assist GPs in management. Consumer brochures will educate the public and provide the necessary information to encourage consumers to speak to their GP regarding their management.

8 STUDY MEDICATION AND SUPPLIES

8.1 Study treatments

Participants in the study will be allocated to one of two treatments: a) Acetylsalicylic acid (ASA) 100 mg: enteric-coated un-scored white tablet or b) placebo: enteric-coated un-scored white tablet with identical appearance. Study medications are provided by Bayer HealthCare. A 100mg dosage was selected as this is the common international dose. The enteric coating will ensure that both active and placebo medication have an identical taste.

Run-in placebo – A box of placebo medication for 4 weeks will be given to participants at the Lifestyle Profile and Screening visit (Visit 1). If for whatever reason a participant cannot attend their Assessments and Eligibility visit (Visit 2) at 4 weeks, they will receive another supply of placebo.

Assessment and Eligibility visit (Visit 2) – Subsequent to this visit, each participant will be provided with a 12 months supply of study medication: either aspirin or placebo.

Annual Visits – At each Annual Visit each participant will be provided with the next 12 months' supply of their allocated study medication.

8.2 Drug packaging

A bulk supply of enteric-coated active and placebo tablets has been provided free of charge by Bayer HealthCare (USA). The medication will be packaged into tablet containers and labeled according to the randomisation code. Participants will be provided with 12 months' supply on each occasion. Packaging will feature the name of the study (ASPREE clinical trial), sponsor (Monash University), supplier (Bayer), batch number, expiry date, contents, the fact that the content is pharmacy medicine for use in clinical trials only, instructions for use, and a warning to keep out of reach of children. Each medication container will be labelled with a pre-printed, unique Medication Identification (ID) Number. Once dispensed, this number will also be recorded in the participant's file in the *Study Drug Accountability Log*.

8.3 Administration of study medication

One tablet is to be taken each morning at breakfast, half an hour before other medications to avoid drug-drug interaction (especially NSAIDs which may diminish the anti-platelet efficacy of ASA).^{76 77}

8.4 Dispensing and randomisation

Medication for the run-in phase will be dispensed to the participant by the RN at Visit 1. Each participant enrolled in the study will be dispensed a box containing 40 placebo tablets. The RN will write the Practice ID number, Subject ID number and participant's initials on the box of run-in medication. When the participant returns for the Assessments and Eligibility visit, the RN will check medication compliance prior to randomisation.

Following the completion of the IVRS randomisation process by the RN (Section 7.1.4), a 12 month supply of study medication will be dispensed at the Clinical Trials Centre pharmacy and posted to the participant. The participant will be asked to confirm receipt of the drug by calling the IVRS automated telephone system. Where confirmation of receipt has not been made within 10 days of dispatch of the drug, the RN will contact the participant to ensure receipt. Attempts to contact the participant will continue until receipt has been confirmed. In the rare instance of missing or undelivered drug, the RN will contact the pharmacy for a re-issue of medication which will be sent to the RN for home delivery to the participant. Subsequent allocation of study medication will be provided in person by the RN at each Annual

Visit. The Medication ID number assigned to the participant will remain the same for the duration of the study. The participant will therefore receive study medication with the same Medication ID number at each visit.

One “*Study Drug Accountability*” Log will be provided for each study participant. These Drug Accountability Logs record the drug dispensed to the participant and drug returned from the participant.

The *Study Drug Accountability* log will record, at minimum, the following information:

- Practice ID number and name
- Subject ID Number and subject initials
- Visit Number
- Medication ID number
- Date dispensed (initials of dispenser)
- Date of medication return (initialed by research staff)
- Number of tablets returned
- Date of medication destruction
- Comments section to allow for explanation of discrepancy, if applicable

8.5 Drug storage

Upon receipt of the study medication from Bayer HealthCare, it will initially be stored at the Clinical Trials Centre pharmacy, at room temperature (15-30°C).

All placebo medication for the run-in phase, as well as subsequent years’ study medication supply, will be distributed to a regional ASPREE centre in each state, and stored in a secured area with restricted access, at room temperature under the supervision of the Regional Medical Coordinator.

All study medication for the randomisation phase will be stored at the Clinical Trials Centre pharmacy until distribution, in a secured area with restricted access, at room temperature under the supervision of the Regional Medical Coordinator for Metropolitan Melbourne.

The receipt, storage, dispensing, accountability and study medication collection, for both the run-in and randomisation phases, are monitored under the responsibility of each state’s Regional Medical Coordinator.

8.6 Drug accountability and dispensing logs

All medication boxes, whether empty or containing unused tablets, must be collected to allow medication compliance to be determined (via a pill count) and to allow for

proper destruction of the medication. Unused tablets are to be returned at the Annual Visit for compliance checking and a new supply of study medication will be issued. Lost medication packs will be replaced and sent to the participant by mail, with all details recorded to allow an audit trail. Tablet counts will be made of all returned medication packs.

Records will be maintained of the product's delivery to each regional ASPREE centre, the inventory at the regional centre, the use by each participant, and the disposition of unused study medication. These records will include dates, quantities, batch numbers, expiry dates and the unique Medication ID numbers assigned to the investigational product(s) and study participants.

Investigators will maintain records that document adequately that study participants were provided the doses specified by the protocol and reconcile all study medication received from the sponsor. The investigator must verify that all unused or partially used drug supplies have been returned by the study participant and that no remaining supplies are in the investigator's possession. Accurate drug records will be achieved through the use of Dispensing Logs.

8.7 Drug disposal

At the end of the study all packages of medication, whether empty or containing unused drugs collected by study staff, will be destroyed according to the Standard Operating Drug Destruction Policy and Procedure of the relevant regional ASPREE centre.

8.8 Emergency code breaking

The treatment identification code for the Medication ID numbers will be securely maintained in the ASPREE Data Management Centre (DMC). The code will only be broken for an individual in the event of a clinical emergency: this will be achieved by phoning independent centres contracted to handle emergency un-blinding. This procedure will ensure that no-one involved in the management or conduct of the study will have access to the randomisation code. The date of, and reason for, the un-blinding will be recorded at the DMC and participants will be encouraged to resume their assigned medication if possible after their immediate condition has resolved. The DSMB will also have access to these details.

8.9 Overdosage of trial medication

A procedure in case of overdose with aspirin is to be specified. The signs of acute

intoxication of ASA are:

- Mild: Nausea, vomiting, sweating, thirst and tachycardia.
- Severe: Fever, CNS disturbances such as convulsions, hallucinations, coma, and respiratory failure.

Treatment:

The initial action is to eliminate the swallowed tablets from the gut by gastric washout and administration of activated charcoal for mild cases (i.e. where no depression of conscious state) and transport to a specialised centre. Severe cases require emergency transport.

9 CONCOMITANT THERAPY

9.1 Oral prescription medications

All oral prescription concomitant medications will be recorded, using the brand name of the drug, on a *Concomitant Medications* CRF including indication for use and start / stop dates.

Any concomitant use of topical ointments, eye drops, ear drops or non-prescription medications (including vitamins, minerals and herbal remedies) will not be recorded on the *Concomitant Medications* CRF.

10 SAMPLE SIZE AND POWER CALCULATIONS

Sample size calculations for the primary endpoint are based on rates of all-cause mortality, clinical diagnosis of dementia and onset of physical disability in Australia. There will be an equal allocation of participants to aspirin and placebo groups.

18,000 participants will be required to have 90% power (two-sided alpha error rate of 0.05) to detect a 10% reduction (risk ratio of 0.90) in the primary endpoint with aspirin. The rationale for this effect size, and further details of the sample size and power calculations are provided in Appendix 2. The sample size was calculated for a univariate Cox proportional hazards regression analysis⁷⁸ using Stata (Stata Statistical Software, Release 10, StataCorp, College Station, TX, 2007) and based on the following assumptions:

- a. The effect of aspirin is described by a hazard ratio of 0.90 in an intention-to-treat analysis. This assumes a stronger underlying effect that will be weakened by cross-over of participants for reasons which include the development of a non-fatal, non-disabling cardiovascular or cerebrovascular

event necessitating aspirin therapy. We expect 5% per annum of placebo-group participants to initiate aspirin use.

- b. Annual dementia incidence rates of 6/1000 for 70-74y age group, 11/1000 (75-79y), 20/1000 (80-84y), 37/1000 (85y+).⁷⁹
- c. Deterioration by 2 points on a Katz ADL scale: annual incidence rate for males = 8/1000, females = 11/1000 (these incidence rates are reduced by 20-25% from the rates observed in the CHS³⁸ which were for incidence of any disability on ADL but in a younger population compared with those in ASPREE).
- d. Age-specific mortality rates based on the 2004 Australian population census (see Table 2, Section 1.2.8 above).
- e. To allow for the analysis to be time-to-first event, individual rates for death, ADL deterioration and dementia can be summed and the sum reduced by 10% to allow for the potential for different events to occur in the same individual.³⁸
- f. Participants will be 45% male and 55% female.
- g. The cohort will consist of approximately 50%, 30%, 15%, 5% in age groups 70-74 years, 75-79 years, 80-84 years, 85 years and over, respectively.
- h. The average "at risk" time will be 4.25 years per participant, which allows for censoring due to the primary endpoint or non-completion of dementia screen or diagnosis, and non-completion of ADLs.

11 ASSESSMENT AND REPORTING OF ADVERSE EVENTS

11.1 Serious Adverse Events

Since aspirin is a well known agent, the approach to safety monitoring will not be exactly the same as that undertaken for a new therapeutic agent. However, serious adverse events (SAEs) considered likely to have resulted from study medication, or from the way in which the study has been designed and conducted, will be reported directly to the ASPREE DMC within 48 hours of becoming aware of the event. DMC will compile the details of such events and present the report to the DSMB.

The original copy of the faxed *Serious Adverse Event* CRF should be kept by the RN in the participant's notes. When the participant's condition is clinically stable the RN should fully complete the SAE form, updating it with the clinical outcome and any relevant test results and forward it by fax or post.

An SAE is defined as any event that:

- Is fatal.
- Is life-threatening.
- Requires hospitalisation or prolongs hospitalisation.
- Results in significant or permanent disability or is incapacitating.
- Requires medical or surgical intervention to prevent permanent impairment/damage.
- Is an accidental or intentional overdose

11.2 Clinically significant bleeding

Clinically significant bleeding is defined as:

- Confirmed cerebral haemorrhages (as defined in Appendix 1: Endpoints and Other Measures) and fatal or life-threatening haemorrhages at other sites that required transfusion, hospitalisation and/or surgery.
- Intracranial haemorrhages other than intracerebral haemorrhagic stroke, i.e. subarachnoid, subdural and extradural haemorrhages demonstrated on computerised tomography (CT) or magnetic resonance imaging (MRI) scanning.

12 ADHERENCE TO ETHICAL, REGULATORY AND ADMINISTRATIVE CONSIDERATIONS

12.1 Ethical Considerations

12.1.1 General

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* and in keeping with local regulations.

ASPREE has ethics approval from the Royal Australian College of General Practitioners Ethics Committee (NREEC 02/22b), Monash University Standing Committee for Ethics in Research Involving Humans (2002/278), the University of Tasmania Human Research Ethics Committee (H0008933) and the ACT Health Research Ethics Committee (ETH.11/07.997). Additionally the principal investigator at each Regional Site may be required to submit the study protocol to their institution Ethics Committee and obtain approval prior to commencing the study. It is the responsibility of the Regional Lead Investigator to determine their own institution's policies.

12.1.2 Information for Participants

Before obtaining consent from the participant they must be informed of the objectives, benefits, risks and requirements of the study, as well as the nature of the test medication. A participant information and consent form should be given to every participant prior to screening.

12.1.3 Informed Consent

The ASPREE Study Investigator (RN or research staff), 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 study including the written participant information and consent form. 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 Informed Consent Form should be signed, name filled in and personally dated by the patient or by the patient'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 patient. 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 Patient Information and Consent Form 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** screening.

12.2 Regulatory Considerations

12.2.1 Financing

The feasibility trial was supported by the National Heart Foundation of Australia. Enteric coated aspirin and matching supply will be provided by Bayer HealthCare. ASPREE has received project grants from the National Health and Medical Research Council, the National Heart Foundation of Australia, the Victorian Cancer Agency, CSIRO, and an educational grant from Bayer HealthCare.

In conjunction with U.S. collaborators, a grant application has also been submitted to the National Institutes of Health, with the support of the National Institute of Ageing, seeking USD \$50 million.

12.2.2 Trial registration

ASPREE is registered on the International Standard Randomised Controlled Trial Number Register (ISRCTN83772183).

12.3 Administrative Organisation

12.3.1 Individual and Committee responsibilities

(Membership details provided in Appendix 3: Committees).

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

Overall management of the trial, organisation of the National Centre, coordination of the Regional Centres and Data Management Centre, and coordination of all aspects of the trial.

Steering Committee

Responsibility for the protocol, any changes to said, and for the general running and financial management of the trial.

International Advisory Committee

External review and advice on the conduct of the trial.

General Practice Advisory Committee

To provide input into the Steering Committee and others on aspects of the trial related to family practice.

Endpoint Adjudication Committee (EAC)

Evaluate individual outcomes blinded to randomised treatment. Relevant documentation will be requested for each endpoint to be validated.

Data Safety and Monitoring Board (DSMB)

Responsibility for quality control of the data, monitoring the progress of recruitment and safety aspects of the trial. The DSMB will also be responsible for supervising / responding to the interim analysis, and will review deaths, SAEs and other data requested on a periodic basis.

The DSMB reports to the Ethics Committees and is supported by the study director and trial statistician.

12.3.2 Publication policy

This policy covers all publications and abstracts originating from ASPREE and any sub-study. The report of the paper will follow the CONSORT (Consolidated Standards of Reporting Trials) guidelines for reporting randomised controlled trials.⁸⁰

Authorship. - Manuscripts and abstracts relating to the ASPREE study must include all current members of the Steering 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 Steering Committee will be named in description of the ASPREE Study Group in each manuscript
- All GP investigators and sub-committee members will be listed on the ASPREE web-site and acknowledged in every publication.

Non-Steering Committee authors utilise the same formula. Disputes about authorship must be notified to the study director to be resolved at the next Steering Committee meeting.

Drafts -Initial and major upgraded manuscripts and abstracts must be circulated to all members of the Steering Committee and any other Committee within ASPREE where relevant (e.g. sub-study). Members have a maximum of one week to send responses.

12.3.3 Sub-studies

Sub-studies must be submitted to and approved by the Steering Committee. They are subject to independent sources of funding being procured and must not impact adversely on the main goals and conduct of the trial. Applications should be made to the Steering Committee and submitted to the study director with a maximum of a five page summary of the rationale and methodology and must include a budget and evidence of funding or a strategy for securing said.

13 DATA MANAGEMENT

13.1 *Data Handling and Record Keeping*

All the results from evaluations conducted during the trial will be recorded on an appropriate CRF for each participant and filed at the relevant regional ASPREE centre. Copies of these CRFs will either be transferred by facsimile to the DMC (where they will be scanned into the study database), or alternatively the data will be uploaded onto the ASPREE web-based portal using the electronic CRFs provided.

Full identification of each participant will be kept by the GP investigator/ RN 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 initialled (see Section 7.2). The RN will fill out or correct the CRFs, in consultation with the GP investigator. The CRFs must be completed during or after each participant visit (or as soon as all data is available, e.g. once pathology results are obtained) and sent via fax to the DMC / uploaded onto the ASPREE web-based portal.

At the end of the trial the GP 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.

13.2 *Quality Control*

All regional ASPREE centres 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 regional 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 that SAEs have been both documented and reported in a timely manner.
- i) Check storage of any study medication and completion of drug accountability logs.
- j) Document all site monitoring visits.

14 REFERENCES

1. EUROASPIRE I and II Group. Clinical reality of coronary prevention guidelines: a comparison of EUROASPIRE I and II in nine countries. EUROASPIRE I and II Group. European Action on Secondary Prevention by Intervention to Reduce Events. *Lancet* 2001;357(9261):995-1001.
2. May GS, Eberlein KA, Furberg CD, Passamani ER, DeMets DL. Secondary prevention after myocardial infarction: a review of long-term trials. *Prog Cardiovasc Dis* 1982;24(4):331-352.
3. Troche CJ, Tacke J, Hinzpeter B, Danner M, Lauterbach KW. Cost-effectiveness of primary and secondary prevention in cardiovascular diseases. *Eur Heart J* 1998;19 Suppl C:C59-65.
4. Jonker C, Comijs HC, Smit JH. Does aspirin or other NSAIDs reduce the risk of cognitive decline in elderly persons? Results from a population-based study. *Neurobiol Aging* 2003;24(4):583-588.
5. Hennekens CH, Hollar D, Baigent C. Sex-related differences in response to aspirin in cardiovascular disease: an untested hypothesis. *Nat Clin Pract Cardiovasc Med* 2006;3(1):4-5.
6. Patrono C, Garcia Rodriguez LA, Landolfi R, Baigent C. Low-dose aspirin for the prevention of atherothrombosis. *N Engl J Med* 2005;353(22):2373-2383.
7. Scheinberg P. Dementia due to vascular disease-a multifactorial disorder. *Stroke* 1988;19:1291-1299.
8. Andrawes WF, Bussy C, Belmin J. Prevention of cardiovascular events in elderly people. *Drugs Aging* 2005;22:859-876.
9. Hayden M, Pignone M, Phillips C, Mulrow C. Aspirin for the primary prevention of cardiovascular events: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 2002;136(2):161-172.
10. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *Br Med J* 2002;324(7329):71-86.
11. Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. *New Engl J Med* 1989;321(3):129-135.
12. Peto R, Gray R, Collins R, Wheatley K, Hennekens C, Jamrozik K, et al. Randomised trial of prophylactic daily aspirin in British male doctors. *Br Med J (Clin Res Ed)* 1988;296(6618):313-316.
13. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* 1998;351(9118):1755-1762.
14. Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. The Medical Research Council's General Practice Research Framework. *Lancet* 1998;351(9098):233-241.

15. Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med* 2005;352(13):1293-1304.
16. Collaborative Group of the Primary Prevention Project. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. Collaborative Group of the Primary Prevention Project. *Lancet* 2001;357(9250):89-95.
17. Baigent C. personal communication. 2004.
18. Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. *The Journal of the American Medical Association* 2006;295(3):306-13.
19. US Preventive Task Force. Aspirin for the primary prevention of cardiovascular events: recommendation and rationale. *Ann Intern Med* 2002;136(2):157-160.
20. Pearson TA, Blair SN, Daniels SR, Eckel RH, Fair JM, Fortmann SP, et al. AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update: Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases. American Heart Association Science Advisory and Coordinating Committee. *Circulation* 2002;106(3):388-91.
21. Nelson MR, Liew D, Bertram M, Vos T. Epidemiological modelling of routine use of low dose aspirin for the primary prevention of coronary heart disease and stroke in those aged > or =70. *Br Med J* 2005;330(7503):1306.
22. Fleming T, Nissen SE, Borer JS, Armstrong PW. Report from the 100th Cardiovascular and Renal Drugs Advisory Committee meeting: US Food and Drug Administration: December 8-9, 2003 Gaithersburg, MD. *Circulation* 2004;109(2):e9004-5.
23. Baigent C. personal communication, 2007.
24. Sturmer T, Glynn RJ, Field TS, Taylor JO, Hennekens CH. Aspirin use and cognitive function in the elderly. *Am J Epidemiol* 1996;143(7):683-91.
25. McGeer PL, Schulzer M, McGeer EG. Arthritis and anti-inflammatory agents as possible protective factors for Alzheimer's disease: a review of 17 epidemiologic studies. *Neurology* 1996;47(2):425-32.
26. Broe GA, Grayson DA, Creasey HM, Waite LM, Casey BJ, Bennett HP, et al. Anti-inflammatory drugs protect against Alzheimer disease at low doses. *Arch Neurol* 2000;57(11):1586-91.
27. in t' Veld BA, Ruitenbergh A, Hofman A, Launer LJ, van Duijn CM, Stijnen T, et al. Nonsteroidal antiinflammatory drugs and the risk of Alzheimer's disease. *N Engl J Med* 2001;345(21):1515-21.
28. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *J Am Med Ass* 2001;286(8):954-9.
29. Topol EJ. Failing the public health--rofecoxib, Merck, and the FDA. *N Engl J Med* 2004;351(17):1707-9.
30. Ross R. Atherosclerosis--an inflammatory disease. *N Engl J Med*

- 1999;340(2):115-26.
31. Kopp E, Ghosh S. Inhibition of NF-kappa B by sodium salicylate and aspirin. *Science* 1994;265(5174):956-9.
 32. Brookmeyer R, Gray S, Kawas C. Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. *Am J Public Health* 1998;88(9):1337-42.
 33. de Craen AJM, Gussekloo J, Vrijisen B, Westendorp RGJ. Meta-Analysis of Nonsteroidal Antiinflammatory Drug Use and Risk of Dementia. *American Journal of Epidemiology* 2005;161(2):114-120.
 34. Kang JH, Cook N, Manson J, Buring JE, Grodstein F. Low dose aspirin and cognitive function in the women's health study cognitive cohort. *BMJ* 2007;334(7601):987.
 35. Whalley LJ, Mowat DHR. Aspirin and cognitive function. *BMJ* 2007;334(7601):961-962.
 36. Newman A, Simonsick E, Naydeck B, Boudreau R, Kritchevsky S, Nevitt M, et al. Association of long-distance corridor walk performance with mortality, cardiovascular disease, mobility limitation, and disability. *JAMA* 2006 295(17):2018-26.
 37. Kuller LH, Shemanski L, Manolio T, Haan M, Fried L, Bryan N, et al. Relationship Between ApoE, MRI Findings, and Cognitive Function in the Cardiovascular Health Study. *Stroke* 1998;29(2):388-398.
 38. Rosano C, Kuller L, Chung H, Arnold A, Longstreth WJ, Newman A. Subclinical Brain Magnetic Resonance Imaging Abnormalities Predict Physical Functional Decline in High-Functioning Older Adults. *J Amer Ger Society* 2005;53(4):649-654.
 39. Harris RE, Beebe-Donk J, Doss H, Burr Doss D. Aspirin, ibuprofen, and other non-steroidal anti-inflammatory drugs in cancer prevention: a critical review of non-selective COX-2 blockade (review). *Oncol Rep.* 2005;13(4):559-583.
 40. Bardia A, Ebbert JO, Vierkant RA, Limburg PJ, Anderson K, Wang AH, et al. Association of Aspirin and Nonaspirin Nonsteroidal Anti-inflammatory Drugs With Cancer Incidence and Mortality. *JNCI Journal of the National Cancer Institute* 2007;99(11):881-889.
 41. Cook NR, Lee IM, Gaziano JM, Gordon D, Ridker PM, Manson JE, et al. Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial. *JAMA* 2005;294(1):47-55.
 42. Australian Institute of Health and Welfare. *Cancer in Australia 2000*. Canberra: AIHW, 2003.
 43. Dube C, Rostom A, Lewin G, Tsertsvadze A, Barrowman N, Code C, et al. The use of aspirin for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force. *Annals of Internal Medicine* 2007;146(5):365-75.
 44. Baron JA, Cole BF, Sandler RS, Haile RW, Ahnen D, Bresalier R, et al. A randomized trial of aspirin to prevent colorectal adenomas. *N Engl J Med* 2003;348(10):891-9.
 45. Sandler RS, Halabi S, Baron JA, Budinger S, Paskett E, Keresztes R, et al. A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. *N Engl J Med* 2003;348(10):883-90.
 46. Chan AT, Giovannucci EL, Meyerhardt JA, Schernhammer ES, Curhan

- GC, Fuchs CS. Long-term use of aspirin and nonsteroidal anti-inflammatory drugs and risk of colorectal cancer. *JAMA* 2005;294(8):914-23.
47. Chan AT, Ogino S, Fuchs CS. Aspirin and the risk of colorectal cancer in relation to the expression of COX-2. *N Engl J Med* 2007;356(21):2131-42.
 48. Flossmann E, Rothwell PM. Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. *Lancet* 2007;369(9573):1603-1613.
 49. Gann PH, Manson JE, Glynn RJ, Buring JE, Hennekens CH. Low-Dose Aspirin and Incidence of Colorectal Tumors in a Randomized Trial. *J Nat Cancer Inst* 1993;85(15):1220-1224.
 50. Chan AT, Manson JE, Feskanich D, Stampfer MJ, Colditz GA, Fuchs CS. Long-term aspirin use and mortality in women. *Arch Intern Med* 2007;167:562-572.
 51. Hernandez-Diaz S, Rodriguez LA. Incidence of serious upper gastrointestinal bleeding/perforation in the general population: review of epidemiologic studies. *J Clin Epidemiol* 2002;55(2):157-63.
 52. Thrift AG, McNeil JJ, Forbes A, Donnan GA. Risk of primary intracerebral haemorrhage associated with aspirin and non-steroidal anti-inflammatory drugs: case-control study. *Brit Med J* 1999;318(7186):759-64.
 53. He J, Whelton PK, Vu B, Klag MJ. Aspirin and risk of hemorrhagic stroke: a meta-analysis of randomized controlled trials. *JAMA* 1998;280(22):1930-5.
 54. Australian Institute of Health & Welfare Heart, stroke and vascular disease - Australian facts 2001. *AIHW cat. No. CVD13*. Canberra: AIHW, National Heart Foundation of Australia, National Stroke Foundation of Australia, 2001.
 55. National Vital Statistics Report. 2005;53(17).
 56. Australian Institute of Health & Welfare. Mortality over the twentieth century in Australia. Trends and patterns in major causes of death. 2006; AIHW cat. no. PHE 73.
 57. Silagy CA, McNeil JJ, Donnan GA, Tonkin AM, Worsam B, Champion K. The PACE pilot study: 12-month results and implications for future primary prevention trials in the elderly. (Prevention with low-dose Aspirin of Cardiovascular disease in the Elderly). *J Am Geriatr Soc* 1994;42(6):643-7.
 58. Mor V, Murphy J, Masterson-Allen S, Willey C, Razmpour A, Elizabeth Jackson M, et al. Risk of functional decline among well elders. *J Clin Epidem* 1989;42(9):895-904.
 59. Teng EL, Chui HC. The Modified Mini-Mental State (3MS) examination. *J Clin Psychiatry* 1987;48(8):314-8.
 60. Wechsler DD. *WAIS-R manual. Clinical and experimental application*, 1990.
 61. Brandt J, Benedict RHB. Hopkins Verbal Learning Test - Revised. Ed: PAR., Odessa, Fla., 2001.
 62. Ross TP. The reliability of cluster and switch scores for the Controlled Oral Word Association Test. *Arch Clin Neuropsychol* 2003;18(2):153-164.
 63. Radloff LS. The CES-D scale: A self report depression scale for research

- in the general population. *Appl Psychol Meas* 1977;1:385-401.
64. Pahor M, Blair SN, Espeland M, Fielding R, Gill TM, Guralnik JM, et al. Effects of a physical activity intervention on measures of physical performance: results of the Lifestyle Interventions and Independence for Elders Pilot (LIFE-P) Study. *J Gerontol Ser A Biol Sci Med Sci* 2006;61(11):1157-1165.
 65. Ware J, Kosinski M, Keller S. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Medical Care* 1996;34(3):220-33.
 66. Wing LM, Reid CM, Ryan P, Beilin LJ, Brown MA, Jennings GL, et al. Second Australian National Blood Pressure Study (ANBP2). Australian Comparative Outcome Trial of ACE inhibitor- and diuretic-based treatment of hypertension in the elderly. Management Committee on behalf of the High Blood Pressure Research Council of Australia. *Clin Exp Hypertens* 1997;19(5-6):779-91.
 67. Reid CM, Wing LM, Graham DH. A new paradigm for funding cardiovascular-outcome research in general practice. The Second Australian National Blood Pressure Study. ANBP2 Management Committee. *Med J Aust* 1998;169(7):349-50.
 68. Reid CM, Ryan P, Nelson M, Beckinsale P, McMurchie M, Gleave D, et al. General practitioner participation in the second Australian National Blood Pressure Study (ANBP2). *Clin Exp Pharmacol Physiol* 2001;28(8):663-7.
 69. Wing LM, Reid CM, Ryan P, Beilin LJ, Brown MA, Jennings GL, et al. A comparison of outcomes with angiotensin-converting-enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med* 2003;348(7):583-92.
 70. Guralnik J, Ferrucci L, Pieper C, Leveille S, Markides K, Ostir G, et al. Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance batter. *J Gerontol Med Sci* 2000;55A:M221-M231
 71. Onder G, Penninx BW, Lapuerta P, Fried LP, Ostir GV, Guralnik JM, Pahor M. Change in physical performance over time in older women: the Women's Health and Aging Study. *J Gerontol A Biol Sci Med Sci* 2002;57(5):M289-93.
 72. Jennison C, Turnbull BW. *Group Sequential Tests with Applications to Clinical Trials*, 2000.
 73. Schulz KF, Grimes DA. Multiplicity in randomized trials I: endpoints and treatments. *Lancet* 2005;365:1348-53.
 74. Sankoh A, D'Agostino R, Huque MS. Efficacy endpoint selection and multiplicity adjustment methods in clinical trials with inherent multiple endpoint issues. *Statistics in Medicine* 2003;22(20):3133-3150.
 75. Molenberghs G, Kenward MG. *Missing Data in Clinical Studies*. Chichester, 2007.
 76. Catella-Lawson F, Reilly MP, Kapoor SC, Cucchiara AJ, DeMarco S, Tournier B, et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N Engl J Med* 2001;345(25):1809-17.
 77. Kurth T, Glynn RJ, Walker AM, Chan KA, Buring JE, Hennekens CH, et al. Inhibition of clinical benefits of aspirin on first myocardial infarction by

- nonsteroidal antiinflammatory drugs. *Circulation* 2003;108(10):1191-5.
78. StataCorp. *Survival Analysis and Epidemiological Tables Manual for Stata Statistical Software: Release 9.0.* . TX: College Station, Stata Corporation, 2006.
 79. Kawas CH, Katzman R. *Epidemiology of Dementia and Alzheimer Disease. In: Alzheimer Disease 2nd Ed, pp.95-116.* 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 1999.
 80. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Clin Oral Investig* 2003;7(1):2-7.
 81. Tombaugh TN. Test-retest reliable coefficients and 5-year change scores for the MMSE and 3MS. *Arch Clin Neuropsychol* 2005;20(4):485-503.
 82. Bland RC, Newman SC. Mild dementia or cognitive impairment: the Modified Mini-Mental State examination (3MS) as a screen for dementia. *Can J Psychiatry* 2001;46(6):506-10.
 83. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders.* 4th ed. Washington, DC: American Psychiatric Association, 1994.
 84. Katula J, Kritchevsky S, Guralnik J, Glynn N, Pruitt L, Wallace K, et al. Lifestyle Interventions and Independence for Elders pilot study: recruitment and baseline characteristics. *J Am Geriatr Soc* 2007;55(5):674-83.
 85. Stewart A, Verboncoeur C, McLellan B, Gillis D, Rush S, Mills K, et al. Physical activity outcomes of CHAMPS II: a physical activity promotion program. *J Gerontol A Biol Sci Med Sci* 2001;56(8):465-70.
 86. Mangani I, Cesari M, Kritchevsky S, Maraldi C, Carter C, Atkinson H, et al. Physical exercise and comorbidity. Results from the Fitness and Arthritis in Seniors Trial (FAST). *Aging Clin Exp Res* 2006;18(5):374-80.
 87. Antman E, Bassand J-P, Klein W, Ohman M, Lopez Sendon JL, Ryden L, et al. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology committee for the redefinition of myocardial infarction. *J Am Coll Cardiol* 2000;36(3):959-969.
 88. WHO. Stroke--1989. Recommendations on stroke prevention, diagnosis, and therapy. Report of the WHO Task Force on Stroke and other Cerebrovascular Disorders. *Stroke* 1989;20(10):1407-31.
 89. Adams HP, Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993;24(1):35-41.
 90. Ebly EM, Schaefer JP, Campbell NR, Hogan DB. Folate status, vascular disease and cognition in elderly Canadians. *Age and Ageing* 1998;27(4):485-91.
 91. Bernick C, Katz R, Smith NL, Rapp S, Bhadelia R, Carlson M, et al. Statins and cognitive function in the elderly: The Cardiovascular Health Study. *Neurology* 2005;65(9):1388-1394.
 92. Wu JH, Haan MN, Liang J, Ghosh D, Gonzalez HM, Herman WH. Impact of antidiabetic medications on physical and cognitive functioning of older mexican americans with diabetes mellitus: a population-based

- cohort study. *Ann Epidemiol* 2003;13(5):369-376.
93. Steffens DC, Krishnan KRR, Crump C, Burke GL. Cerebrovascular Disease and Evolution of Depressive Symptoms in the Cardiovascular Health Study. *Stroke* 2002;33(6):1636-1644.
 94. Sato R, Helzlsouer KJ, Comstock GW, Hoffman SC, Norkus EP, Fried LP. A cross-sectional study of vitamin C and cognitive function in older adults: the differential effects of gender. *J Nutr Health Aging*. 2006;10(1):37-44.
 95. Fried L, Young Y, Rubin G, Bandeen- Roche K, Collaborative. WI. Reported preclinical disability identifies older women with early declines in performance and early disease. *J Clin Epidemiol*. 2001;54(9):889-901.
 96. Alexander N, Guire K, Thelen D, Ashton-Miller J, Schultz A, Grunawalt J, et al. Self-reported walking ability predicts functional mobility performance in frail older adults. *J Am Geriatr Soc* 2000;48(11):1408-13.
 97. Tinetti M, Inouye S, Gill T, et al. Shared risk factors for falls, incontinence, and functional dependence. Unifying the approach to geriatric syndromes. *JAMA* 1995;273:1348-1353.
 98. Rantanen T, Guralnik J, Ferrucci L, et al. Co-impairments as predictors of severe walking disability in older women. *J Am Geriatr Soc* 2001;49:21-27.
 99. Cesari M, Kritchevsky S, Penninx B, Nicklas B, Simonsick E, Newman A, et al. Prognostic value of usual gait speed in well-functioning older people--results from the Health, Aging and Body Composition Study. *J Am Geriatr Soc*. 2005 53(10):1675-80.
 100. Perera S, Mody S, Woodman R, Studenski S. Meaningful change and responsiveness in common physical performance measures in older adults. *J Am Geriatr Soc* 2006;54(5):743-9.
 101. Fried L, Tangen C, Walston J, Newman A, et al., on behalf of the CHSCR Group. Frailty in Older Adults. Evidence for a Phenotype. *J of Gerontology Series A: Biol and Med Sciences* 2001;56:M146-M157.
 102. Neuhaus JM, Kalbfleisch JD. Between-and within-cluster covariate effects in the analysis of clustered data. *Biometrics* 1998;54:638-645.
 103. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MMB. Silent Brain Infarcts and the Risk of Dementia and Cognitive Decline. *N Engl J Med* 2003;348(13):1215-1222.
 104. Australian Institute of Health & Welfare C. Mortality over the twentieth century in Australia. Trends and patterns in major causes of death. 2006; AIHW cat.no. PHE73.
 105. <http://www.aihw.gov.au/cognos/cgi-bin/ppdscgi.exe?DC=Q&E=/Cancer/cancerageratesv5>.

APPENDIX 1.

ENDPOINTS AND OTHER MEASURES

1. Primary Endpoint:

Death from any cause or incident dementia or persistent physical disability.

These categories of disability are defined, respectively, as a clinical diagnosis of dementia by DSM-IV criteria; or a progression by at least 2 intervals on a 5-point scale of, or a loss of ability to perform independently, any one of 6 Katz ADLs.

1.1 All-cause mortality

Death certification and post mortem report.

1.2 Incidence of all-cause dementia

The trigger for a dementia assessment is a 3MS test score of ≤ 77 , or a reliable minimum change score of 10 points or more from baseline or the last test will trigger referral for dementia assessment^{59 81 82} with the cut-off being based on a regression model developed from the referenced community-based studies. This is necessary because as a predictor of dementia the change in an individual's 3MS is not linear across the range of scores (i.e. a change from 100 to 90 is not equal to a change from 90 to 80 or 80 to 70). Based on WHIMS data, participants who score below education-specific cut points of <88 (>8 yrs education) and <80 (<8 yrs education) provide positive prediction probability of >0.90 for dementia.

The diagnosis of incident dementia in ASPREE will be made on the basis of Diagnostic and Statistical Manual for Mental Disorders, American Psychiatric Association (DSM-IV) criteria. A "tick-a-box" proforma covering these criteria will be issued to each assessing clinician. Australian participants scoring ≤ 77 on the 3MS will be clinically evaluated for incident dementia by geriatricians and neurologists experienced in the area of dementia assessment. Payment for this would be covered by Australia's universal health coverage program.

In the U.S., participants scoring ≤ 77 on the 3MS will be referred for further cognitive assessment to a neurologist, geriatrician, or psychiatrist experienced in the diagnosis of dementia. This is a Medicare-covered indication for assessment and each of the four U.S. Hubs and their field sites in ASPREE have access to dementia or memory assessment clinics, or an Alzheimer's Disease Research Center for these participant referrals. The clinical cognitive assessments for all referred participants will be reviewed and all diagnoses of dementia or mild cognitive impairment will be adjudicated by two individuals with expertise in dementia (neurologist or geriatrician) from the Endpoint Committee. Based on published age-specific incidences of dementia⁷⁹ and the expected age structure of the study population at recruitment, we expect that ~360 individuals of the 4,000 participants to be recruited in the U.S. will be referred for full cognitive assessment.

A clinical diagnosis of dementia noted in the medical records of any participant not already referred for dementia assessment will also trigger an Endpoint Case Report Form. The Endpoint Committee will use DSM-IV criteria to confirm dementia⁸³ or ask the field center to refer the participant for a formal dementia assessment. Diagnostic features include: memory impairment and at least one of the following: aphasia, apraxia, agnosia, disturbances in executive functioning. In addition, the cognitive impairments must be severe enough to cause impairment in social and occupational functioning. Importantly,

the decline must represent a decline from a previously higher level of functioning. Finally, the diagnosis of dementia should NOT be made if the cognitive deficits occur exclusively during the course of a delirium. Classification of vascular dementia *versus* Alzheimer's disease or mixed dementia will not be requested, due to the lack of validated, clearly defined diagnostic criteria for vascular dementia.

1.3 Progression of physical disability for activities of daily living

Self-reported ability to perform each of the six Katz ADLs independently will be collected at baseline and annually, as a dichotomous outcome as it is most often used to define the incidence of disability, which occurs at a rate of about 10% per year in this age group³⁸. The ADL activities include walking, bathing, dressing, transferring from a bed or chair, using the toilet, and eating. For these activity measures, we will use questions adapted from the LIFE questionnaire, a 25-item, self-report disability questionnaire developed at WFUHS for the NIA-sponsored LIFE study.⁶⁴ It has been used in multiple studies.⁸⁴⁻⁸⁶ Measurements of perceived difficulty in general activities of daily living during the previous month will be recorded across the range of (1) no difficulty, (2) a little difficulty, (3) some difficulty, (4) a lot of difficulty, or (5) unable to perform, as well as whether they are able to perform the activity without assistance. On this five-point scale, a progression by at least 2 intervals for any one of the ADL's, or a requirement for assistance to perform an ADL, will be deemed a loss of function. We will require persistence of this level of disability for at least 6 months to consider the participant as having reached this component of the primary endpoint. This will be confirmed at the subsequent 6 month telephone call after the initial report. If the subsequent contact is missing, a proxy will be contacted for this information. If death precedes this follow-up contact, the death will be counted as the endpoint. If the subsequent contact is missed, but followed by death, persistent disability will be presumed.

2. Secondary Endpoints:

1. All-cause mortality
2. Fatal and non-fatal cardiovascular events including a) coronary heart disease death, b) non-fatal myocardial infarction (MI), c) fatal and non-fatal stroke and d) hospitalization for heart failure.
3. Fatal and non-fatal cancer, excluding non-melanomatous skin cancer
4. Dementia
5. Cognitive decline
6. Physical disability
7. Major hemorrhagic events

2.1 All-cause mortality

As described above in 1.1

2.2 Fatal and non-fatal cardiovascular events including a) Coronary heart disease death, b) non-fatal MI, c) fatal and non-fatal stroke and d) hospitalization for heart failure.

a) Coronary heart disease death - MI, sudden cardiac death, rapid cardiac death (death after possible MI), cardiac failure death (with coronary cause) and other coronary death.

- *Myocardial infarction* - Autopsy or death certificate diagnosis, with definitive or suspected diagnosis of MI within 4 weeks of death.
- *Sudden cardiac death* - Death occurring within one hour of the onset of new cardiac symptoms (ischemic chest symptoms or sudden collapse) or unwitnessed death after last being seen without new cardiac symptoms, and in each case, without any coronary disease (clinically or at autopsy) that could have been rapidly fatal.
- *Rapid cardiac death (death after possible MI)* - Death within 1-24 hours of the onset of severe cardiac symptoms unrelated to other known causes. Death in hospital with possible MI (i.e. participants who have had typical ischemic pain and whose ECG and

enzyme results fulfil the criteria for definitive MI and in whom there is no good evidence for another diagnosis for the event).

- *Cardiac failure (with coronary cause)* - Death due to heart failure (prior NYHA Class III-IV dyspnea), without any defined non-coronary cause.
- *Other coronary death* - Any death where the underlying cause is certified as coronary (and where there is no evidence of non-coronary cause of death, clinically or at autopsy).

b) Non-fatal MI – (American College of Cardiology & European Society of Cardiology definition).⁸⁷

Criteria for acute, evolving or recent MI. Either one of the following criteria satisfies the diagnosis for an acute, evolving or recent MI:

(1) Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:

- ischemic symptoms;
- development of pathologic Q waves on the ECG;
- ECG changes indicative of ischemia (ST segment elevation or depression);

or

- coronary artery intervention (e.g. coronary angioplasty).

(2) Pathologic findings of an acute MI.

Criteria for established MI. Any one of the following criteria satisfies the diagnosis for established MI:

- Development of new pathologic Q waves on serial ECGs. The patient may or may not remember previous symptoms. Biochemical markers of myocardial necrosis may have normalized, depending on the length of time that has passed since the infarct developed.
- Pathologic findings of a healed or healing MI.

c) Fatal and non-fatal stroke – Fatal stroke will be defined as any death due to the rapid onset of a new neurological deficit attributed to obstruction or rupture in the intra-cranial or extra-cranial cerebral arterial system. Stroke will be defined according to the World Health Organization (WHO) definition as ‘rapidly developing clinical signs of focal (or global) disturbance of cerebral function lasting more than 24 hours (unless interrupted by surgery or death) with no apparent cause other than of vascular origin’.⁸⁸ This definition excludes cases of primary cerebral tumor, cerebral metastasis, subdural hematoma, post seizure palsy, brain trauma, and transient ischemic attack. In Australia and the U.S., many suspected strokes occurring in non-institutionalized patients are investigated by imaging with CT and/or MRI scanning. Where available, these reports will be considered in the endpoint determination.

Because hemorrhagic stroke is both an endpoint and an adverse event, sub-classification will be used for strokes. Ischemic stroke is defined as a stroke for which a CT scan performed within 28 days of the onset of symptoms showed an area of low attenuation or a normal appearance in the vascular territory that corresponded to the recent symptoms and signs; or MRI showed a clinically relevant area of increased signal on diffusion weighted imaging, a slight hypointensity with or without mass effect on T1-weighted images and a bright area of hyper intensity with or without mass effect on T2-weighted images evidence of recent infarction or on diffusion weighted MRI imaging. Alternatively cerebral infarction may be confirmed by autopsy. The TOAST classification for subtype of acute ischemic stroke will be utilized,⁸⁹ in which both clinical features and ancillary tests (laboratory, radiology, and ultrasonography) are used to categorize five subtypes:

1. large artery atherosclerosis (embolus/thrombosis)
2. cardio embolism (high risk/medium risk)
3. small-vessel occlusion (lacunae)
4. stroke of other determined etiology

5. stroke of undetermined etiology
 - a. two or more causes identified
 - b. negative evaluation
 - c. incomplete evaluation

A summary of the classification for ischemic stroke is shown in Table 1.

Features	Subtype			
	Large-artery atherosclerosis	Cardio embolism	Small-artery occlusion (lacunae)	Other causes
Clinical				
Cortical or cerebellar dysfunction	+	+	-	+/-
Lacunar syndrome	-	-	+	+/-
Imaging				
Cortical, cerebellar, brain stem, or subcortical infarct >1.5 cm	+	+	-	+/-
Brain stem, or subcortical infarct <1.5cm	-	-	+/-	+/-
Tests				
Stenosis of extracranial internal carotid artery	+	-	-	-
Cardiac source of emboli	-	+	-	-
Other abnormality on tests	-	-	-	+

Table 1. Features of Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification of subtypes of ischemic stroke.⁸⁹

Haemorrhagic stroke - is defined as a stroke in which a CT scan demonstrates an area of hyperdensity within the brain parenchyma with or without extension into the ventricles or subarachnoid space or, for scans performed beyond 1 week, an area of attenuation with ring enhancement after injection of contrast; MRI showing an area of hypointensity or isointensity on T1-weighted images or an area of marked hypointensity on gradient echo and T2-weighted images, or by autopsy demonstrating the origin of the hemorrhage as the cerebral parenchyma. Rarer causes and sites of intracerebral hemorrhage such as underlying arteriovenous malformation and spinal cord hemorrhage will be documented. Distinction between ischemic and haemorrhagic stroke can only be made with appropriate imaging. CT scanning is now undertaken as part of the investigation of most cases of stroke in Australia. Results of such imaging will be sought routinely by the ASPREE investigators for presentation to the endpoint committee.

d) Hospitalisation due to cardiac failure - Hospital discharge diagnosis of cardiac failure will trigger an assessment by the endpoint committee. Hospitalisation for heart failure is defined as an unplanned overnight stay, or longer, in a hospital environment (emergency room, observation unit or inpatient care) or similar facility. Heart failure is defined as a patient having typical symptoms (eg, dyspnoea, fatigue) that can occur at rest or on effort that is characterized by objective evidence of an underlying structural abnormality or cardiac dysfunction that impairs the ability of the ventricle to fill with or eject blood (particularly during exercise). The diagnosis of heart failure may be further strengthened by a beneficial clinical response to treatment(s) directed towards amelioration of symptoms associated with this condition.

2.3 Incidence of fatal and non-fatal cancer (excluding non-melanomatous skin cancer)

Morbidity and mortality from all-incident cancers (excluding non-melanomatous skin cancers) confirmed histologically will constitute a secondary endpoint. Mandatory reporting of all new cancers to state-based tumour registries in Australia, along with multiple mechanisms which are in place to ensure this data is complete (including routine

surveillance of hospital discharge records and death certificates) will ensure robust cancer incidence data. In Australian and U.S. aged populations colon cancer will be a predominant incident cancer, being the second-leading cause of cancer related death. Because a common presentation of colon cancer is with rectal bleeding it is possible that the use of aspirin may cause ascertainment bias. However, this has not been documented in any of the intervention studies to date. In particular in the Nurses' Health Study⁴⁶ the investigators controlled for use of screening endoscopy in all of the multivariate analyses. They also evaluated the influence of aspirin among women who did not report having a positive fecal occult blood test result or did not undergo screening endoscopy. Among such women, the influence of aspirin was not materially altered.

2.4 Dementia

Clinical assessment as described above in 1.2.

2.5 Cognitive decline

We will use a decrease in scores adjusted for education level attained to identify incident mild cognitive impairment and dementia (see above in 1.2) with the 3MS. A decrease in 3MS score of ≥ 10 points will be used as a measure of clinically significant cognitive decline.^{59 81 82} The 3MS incorporates the original Mini Mental State Examination (MMSE), but also includes a measure of verbal fluency (often impaired early in Alzheimer's disease), a similarities subtest (testing an aspect of executive function), and delayed recall/recognition of the word list for memorization, as well as two further orientation questions. The 3MS has been used in a number of large interventional studies.⁹⁰⁻⁹²

2.6 Physical disability

A secondary endpoint will be reached with a loss of 2 levels on the 5-level scale of one Katz ADL (as described above in section 1.3.)

2.7 Major haemorrhagic events - Clinically significant bleeding

Gastrointestinal haemorrhages or haemorrhages at other sites that required transfusion, hospitalization and or surgery. Source information from clinical case notes and hospital medical records related to these events will be collected and sent to the ASPREE DMC.

3. Other Measures:

3.1 Cognitive function

In addition to the 3MS, the following depression and cognitive function tests will be administered at baseline and biennially.

a) Depression - The CES-D is administered in conjunction with the 3MS to ensure a low score on the cognitive function test is not the result of depression. A modified version of 10 questions of the CES-D will be used. The modification omits questions related to lifestyle that are covered by the LIFE questionnaire. A score of 8 or higher on the 30 point CES-D 10 scoring is deemed clinically significant.⁹³ Any such score will be communicated back to the family physician, and would typically result in a clinical assessment. However, it is judged impractical to rely on the resultant clinical assessments being sufficiently standardized across sites, countries and types of practice (family physicians *versus* psychiatrists) in such a large trial to substitute clinical assessments for CES-D scores.

b) DSST – An additional non-language based test of cognitive function, the Digit Symbol Substitution Test (DSST), is also included in this assessment as a measure of executive function, specifically of processing speed and activation.⁶⁰ The DSST has been used longitudinally in other large-scale studies⁹⁴ and has been shown to be sensitive to both age-related cognitive decline and the increasing load of cerebrovascular disease. The DSST does not use the alphabet. It is therefore not likely to penalize illiterate or semi-literate individuals. It is also easy to administer and score, and has both high 'ceiling' and

low ‘floor’ effects, making it useful in assessment across a wide range of abilities.

c) Hopkins Verbal Learning Test- Revised (HVLTR) – The HVLTR⁶¹ is a test of immediate and delayed recall, and delayed recognition. It has been widely used in previous studies of cognitive impairment. It is sensitive to change, has validated age and education- adjusted norms, and takes less time to administer than other word lists frequently used to test memory (such as the Rey Altered Verbal Learning Test).

d) Single Letter Fluency Test (SLFT) – The SLFT (or Controlled Oral Word Association Test – COWAT⁶²) is a measure of executive function and verbal fluency. Patients are asked to generate as many words as possible beginning with specific letters (e.g., F, A, S).

3.2 Physical Performance

Both performance-based and self-report instruments will be used to measure physical function. These detailed assessments will be carried out every other year, alternating with the cognitive assessment measures. Performance- based measures are very sensitive to change and can detect early decline prior to the onset of disability in activities of daily living (ADL).⁷⁰ They have less of a ceiling effect than other measures of function or self-reported function and, as continuous variables provide more power to assess treatment effect. Small differences in performance (0.1 m/sec in gait speed)⁷⁰ are related to important subsequent mortality risk, so that prevention of decline would represent an important treatment effect of aspirin. Self report of increased difficulty with an activity identifies early declines in performance measures, and incident mobility disability.^{95 96} Limitations in or inability to perform ADL and mobility tasks reflect the subject’s perception of their ability to perform in their own environment, and correlate moderately with performance- based measures,⁹⁶ and therefore are considered to be complementary. Self- report instrumental activities of daily living (IADL) disability measures assess ability to carry out functions such as cooking, shopping and taking medication, which are also important for maintenance of independent living.

For these activity measures, we will use questions adapted from the LIFE questionnaire (as described above in 1.3). This questionnaire has been used in multiple studies.⁸⁴⁻⁸⁶ It consists of 5 activity subscales: basic ADLs, mobility, transferring, instrumental and upper extremity. As described above for the ADL’s, perceived difficulty in general activities of daily living during the previous month will be measured across the range of (1) no difficulty, 2) a little difficulty, 3) some difficulty, 4) a lot of difficulty, or 5) unable to perform. We will also examine directly the change in the continuous disability score, grip strength and gait speed, to determine whether aspirin will attenuate age-related decline in these measures of physical function.

a) Performance based measures

Two performance-based measures will be used: grip strength and gait speed for usual walking. These two measures are each strong independent predictors of mortality and disability, and very sensitive to change.^{70 71} Both can be assessed within 10 minutes and in either the home or clinic settings.

Hand grip strength will be measured in kilograms using a handheld isometric dynamometer (Jaymar; JLW Instruments, Chicago, Illinois). Grip strength of each hand will be measured as the best of two trials. In the Women’s Health and Aging Study, the mean baseline grip strength was 19.7 (± 5.9) kg, and declined by 1.4 (± 4.3) kg, or 6.8% over 3 yrs.⁷¹

Gait speed will be assessed as the time in seconds to walk 3 metres (8 feet) at the participant’s usual walking pace from a standing start. Time on the faster of two walks will be used to define scores.⁷⁰ Gait speed will be examined as a continuous variable. A walking speed lower than 0.42 m/s is considered to represent severe walking disability.⁹⁷⁹⁸ Speeds of less than 1.0 m/sec are predictive of mortality and hospitalization⁹⁹ and

changes of >0.1 m/sec related to significant perceived decline.¹⁰⁰

b) Self-report measures (using the LIFE Questionnaire)

Mobility activities – walking one block, walking a quarter of a mile (about 2 or 3 blocks), walking one mile, climbing one flight of stairs, walking in the grocery aisle without sitting or leaning on the cart, getting in and out of a car.

Instrumental ADLs - doing light housework, preparing own meals, managing own money, using the telephone, doing errands, taking care of a family member, visiting relatives or friends, participating in community activities, taking own medications.

Upper extremity activities (tertiary) - lifting heavy groceries or 10 pounds, raising arms overhead, lifting heavy objects, gripping with hands.

c) Frailty measures

Measures of gait speed and grip strength (as measured in performance measures above) will also be combined with a single item question on fatigue/energy level (from the SF-12 below). Weight loss will be assessed from the annual clinic assessment of weight. We will ask a single item regarding physical activity, adapted from the LIFE study. These few items can be combined to create an assessment of frailty using the Fried criteria.¹⁰¹ This will be assessed every other year in conjunction with the performance measures.

3.3 Maintaining quality of life

Quality of life will be assessed annually using the Short Form 12 (SF-12) item questionnaire, which includes physical functioning, mental health, role functioning. (both physical and emotional), health perceptions in the last year, energy level and pain level.⁶⁵ This will provide a basic assessment of functioning on a more frequent basis than the more detailed physical function assessments which, as stated above, will be conducted every other year.

3.4 Haemoglobin

Measurement of hemoglobin levels will be undertaken at baseline and annually.

3.5 Hospitalisation

Total hospitalisations and hospitalisation for reasons other than endpoints will be collected.

APPENDIX 2.

DETAILS OF SAMPLE SIZE AND POWER CALCULATIONS

For the primary endpoint, a sample size has been calculated that gives the number of primary endpoint events required for ASPREE to have 90% power for their subsequent analysis by a univariate Cox proportional hazards regression model. To estimate the number of participants required to yield these events, assumptions are made for (i) the event rates that will be seen in ASPREE participants and (ii) the duration of participant follow-up during the study. Having obtained a sample size for the primary endpoint we examine the power or effect size that this number of participants gives us for each secondary endpoint. Hence, assumptions are also required for the event rates of secondary endpoints.

The study will have a 1:1 aspirin:placebo group allocation ratio.

All power and sample size calculations were performed with a two-sided alpha error rate of 0.05 for a univariate Cox proportional hazards regression analysis of time to first event using the 'stpower cox' command in Stata (Stata Statistical Software, Release 10, StataCorp, College Station, TX, 2007).

Assumptions used for the sample size and power calculations include:

- Participants will be approximately 50%, 30%, 15%, 5% in age groups 70-74 years, 75-79 years, 80-84 years, 85 years and over, respectively.
- Participants will be 45% male and 55% female.
- Based on experience with ANBP2, the effect of clustering due to recruitment by region and enrolling GP or clinical research site will be minimal and no explicit adjustment to the number of participants needs to be made. In any case, since randomisation is at the individual participant level, treatment effect is a within-cluster comparison and this protects against any concern over loss of power due to clustering.¹⁰²
- Accrual of participants is over approximately a 2 year period with an average of 5 years of follow-up per participant.
- Rates are assumed for participants based on their age at entry to the study. Further, the rates are assumed to stay constant throughout participants' follow-up.

1. Primary Outcome

ASPREE is designed to have 90% power to detect an effect of aspirin as described by a hazard ratio of 0.90 in an intention-to-treat analysis. Aspirin has dual mechanisms of action likely to affect the primary endpoint. Anti-prostaglandin effects are postulated to affect atherogenesis and carcinogenesis and acetylation within platelets is likely to affect atherothrombotic and hemorrhagic events.⁶ We would propose that the latter mode of action is likely to have a dominant effect on the primary endpoint due to lag time in the former⁴⁶ and vascular events being the major determinant of morbidity (including dementia^{6 103} and mortality in the aged.⁴⁶ The Anti-thrombotic Trialists Collaboration has provided us with a meta-analysis of all six primary prevention trials by age categories which shows that the point estimate of the benefit of aspirin over no aspirin treatment on all-cause mortality alone is 0.95 with wide confidence intervals (95% CI: 0.70 – 1.14) in those subjects aged 70 years and over.²³ The point estimate of aspirin's effect on adverse cardiovascular disease events from the same meta-analysis is 13% (95% CI: 0.65 – 1.16). This suggests that a 10% treatment effect for aspirin is plausible. These studies experienced cross-over of participants from one treatment group to the other for reasons which include the development of a non-fatal, non-disabling cardiovascular or cerebrovascular event necessitating aspirin therapy.

Similarly, we expect 5% per annum of placebo-group participants to initiate aspirin use with a lower rate of the aspirin-group participants ceasing use of aspirin. Hence the underlying effect of aspirin will be even stronger than the hazard ratio of 0.90 that we anticipate observing in an intention-to-treat analysis.

The following assumptions have been made for event rates for the primary endpoint of death from any cause or incident dementia or persistent physical disability (the latter two events defined as follows: for dementia, a clinical diagnosis of dementia by DSM-IV criteria will be used; physical disability will be defined as the inability to perform independently, or a progression by at least 2 intervals on a 5-point scale, any one of 6 Katz ADLs).

- a. Dementia annual incidence rates will be 6 per 1000 for the 70-74y age group, 11/1000 (75-79y), 20/1000 (80-84y), 37/1000 (85y+).⁷⁹
- b. Deterioration by 2 intervals on a Katz ADL; annual incidence rate for males = 8/1000, females = 11/1000 (these incidence rates are reduced by 20-25% from the rates observed in the CHS³⁸ which were for incidence of any disability on ADL but in a younger population compared with those in ASPREE).
- c. Age specific annual mortality rates from the 2004 Australian population census⁵⁶ (source=ICD10 ALL, Australia, 1907–2004 - General Record of Incidence of Mortality, GRIM¹⁰⁴) are relevant. For males these were 26.66/1000 person years for the 70-74y age group, 44.84/1000 person years (75-79y), 76.43/1000 person years (80-84y), 156.36/1000 person years (85y+), and for females the corresponding rates were 14.68/1000 person years (70-74y), 27.23/1000 person years (75-79y), 51.08/1000 person years (80-84y), 128.93/1000 person years (85y+).
- d. Assume participants will be healthy relative to their same-aged population counterparts and that mortality rates will be 50% lower than the general population rates in assumption (c) above.
- e. To allow for the analysis to be time to first event, individual rates for death, ADL deterioration, and dementia can be summed and the sum reduced by 10% to allow for the potential for different events to occur in the same person.³⁸
- f. Using assumptions (a) to (e) above the primary endpoint rate in the placebo group will be 54.1 per 1000 person years.

The study aims for 5 years average follow-up per participant and for the primary endpoint this "at risk" time for occurrence of a first primary endpoint event will be reduced to an average of 4.25 years per participant. The reasons for this reduction include censoring due to the occurrence of a primary endpoint, loss to follow-up for death (which is expected to be extremely low due to access to mortality statistics through National Death Index records), non-completion of dementia screen or diagnosis, and non-completion of ADLs. In total, we assume that 5% of participants per year will have an occurrence of the primary endpoint or have insufficient follow-up to enable assessment of their primary endpoint status.

On the basis of these assumptions, 3787 primary endpoints in 18,025 participants will be required to have 90% power (two-sided alpha error rate of 0.05) to detect a 10% reduction (risk ratio of 0.90) in the primary endpoint with aspirin.

The sample size for the primary endpoint of death from any cause or incident dementia or persistent physical disability will be 18,000 participants.

2. Secondary Outcomes

1. All-cause mortality

Anticipated rates of all-cause mortality are given above under the primary endpoint sample size calculation. A sample size of 18,000 provides 90% power to detect a hazard ratio of 0.791 comparing the aspirin group with placebo in an intention-to-treat analysis (all other assumptions as for primary endpoint).

2. Fatal and non-fatal cardiovascular events including a) coronary heart disease death, b) non-fatal myocardial infarction, c) fatal and non-fatal stroke and d) hospitalization for heart failure

- Based on the experience in other primary prevention trials in the elderly²³ it is assumed that the rate of CVD events, (including hemorrhagic stroke; see below) will be 17.0 per 1000 person-years (70-74y age group), 25.0 per 1000 person-years (75-79y), 38.0 per 1000 person-years (80y+).
- These event rates lead to an overall annual rate of 23.6/1000 person years from which an annual rate of 1.2/1000 person years for hemorrhagic stroke⁵³ is subtracted. Hence we expect this secondary endpoint to have an annual rate of 22.4/1000 in the placebo group.
- Assume that there will be an annual loss to follow-up of 3% of participants per annum for this endpoint due to other causes of mortality and, based on ANBP2, an expected very low rate of non-assessment of non-fatal CVD status. This corresponds to an average of 4.7 years per participant at-risk time.

A sample size of 18,000 participants gives 90% power to detect a 14.5% reduction in CVD event risk (hazard ratio 0.855) in an intention-to-treat analysis based on the above assumptions.

3. Fatal and non-fatal cancer, excluding non-melanomatous skin cancer

For a sample size of 18,000 subject to 3% per annum drop out, the study will have 90% power to detect the following hazard ratios for the comparison of intervention to placebo in an intention to treat analysis (assuming rates in the placebo group as described and other assumptions as for primary endpoint);

	Rates with placebo	Hazard ratio
Colorectal cancer	3.56 per 1000 person years ¹⁰⁵	0.659
All cancer	8.70 per 1000 person years ¹⁰⁵	0.773

4. Dementia

Anticipated rates of dementia are given above under the primary endpoint sample size calculation. A sample size of 18,000 provides 90% power to detect a hazard ratio of 0.791 comparing the aspirin group with placebo in an intention-to-treat analysis (all other assumptions as for primary endpoint).

5. Cognitive decline

Our primary interest is the difference between placebo and aspirin groups in average 3MS rate-of-change from baseline to the end of 5 years of follow-up. Because this measurement is on a continuum, only 5200 participants are required to provide 90% power to detect a clinically relevant 1 point smaller decline over 5 years in the mean 3MS score of the aspirin group than the placebo group. Even assuming the worst-case scenario for variability in 3MS measurements (for example SD=10) and the strength of correlation between baseline and end-of-study measurements the sample size of 18,000 participants will be more than sufficient to have 90% power to detect a 1-point smaller decline in this secondary endpoint.

6. Physical disability

Anticipated rates of deterioration by 2 intervals on a Katz ADL 5-level range are given above under the primary endpoint sample size calculation. A sample size of 18,000 provides 90% power to detect a hazard ratio of 0.797 comparing the aspirin group with placebo in an intention-to-treat analysis (all other assumptions as for primary endpoint).

7. Major haemorrhagic events

We anticipate rates of major bleeds of 11 events per 1000 person-years in the placebo group based on:

- Haemorrhagic stroke rate of 1.2 per 1000 person years.⁵³
- Serious upper GI complications: between 2 and 14 events per 1000 person-years for those over 70 years, increasing sharply with age.^{6 53}

Given a total sample size of 18,000, we have 90% power to detect a hazard ratio of 1.282 comparing the aspirin group with placebo in an intention-to-treat analysis where compliance with medication and drop-out are assumed as for the primary endpoint.

APPENDIX 3. COMMITTEES

STEERING COMMITTEE

Professor David Ames MBBS MD BA
MRCP FRCP
Department of Psychiatry
University of Melbourne
Normanby House, St. Georges Hospital,
283 Cotham Road, Kew, VIC 3101
dames@unimelb.edu.au

Professor Lawrence J Beilin MBBS MD MA
FRCP FRACP FCSANZ
Chairman,
Department of Internal Medicine
Royal Perth Hospital,
Perth, Western Australia
lbeilin@cyllene.uwa.edu.au

Professor Geoffrey A Donnan MBBS MD
FRACP FRCP
Director
National Stroke Research Institute
Austin & Repatriation Medical Centre
Level 1, Neurosciences Building
Gate 10, Banksia Street
Heidelberg West VIC 3081
gdonnan@unimelb.edu.au

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

Professor Colin I Johnston MBBS FRACP
MD FAHA
Professor of Medicine
Baker Heart Research Institute
Melbourne VIC 8008
colin.johnston@baker.edu.au

Professor Elsdon Storey MBBS D.Phil
FRACP
Professor of Neuroscience and Director,
Department of Neurosciences and Van
Cleeef Roet Centre for Nervous Disease,
Department of Medicine
Monash University, Alfred Hospital
Melbourne 3004
elsdon.storey@med.monash.edu.au

Professor Henry Krum MBBS PhD FRACP
Professor and Director,
NHMRC Centre of Clinical Research
Excellence in Therapeutics
Department of Epidemiology and Preventive
Medicine, Monash University / Alfred
Hospital, Melbourne 3004
henry.krum@med.monash.edu.au

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

Professor Mark R Nelson MBBS(Hons)
MFM FRACGP FAFPHM PhD
Chair of Discipline of General Practice
School of Medicine
University of Tasmania
Private Bag 33, Hobart, Tasmania 7001
Mark.Nelson@utas.edu.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

Professor Andrew Tonkin MBBS MRACP
FRACP MD
NHMRC Centre of Clinical Research
Excellence in Therapeutics
Department of Epidemiology and
Preventive Medicine
Monash University / Alfred Hospital
Melbourne 3004
andrew.tonkin@med.monash.edu.au

A/Prof Rory Wolfe BSc Grad Cert Stats
PhD, Biostatistician
Department of Epidemiology and
Preventive Medicine
Monash University / Alfred Hospital
Melbourne 3004
rory.wolfe@med.monash.edu.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

INTERNATIONAL ADVISORY COMMITTEE

Dr Colin Baigent BA MBBS
Reader in Clinical Epidemiology
Clinical Trial Service Unit
Richard Doll Building
Oxford University
Old Road Campus
Roosevelt Drive
Oxford OX3 7LF, UK
colin.baigent@ctsu.ox.ac.uk

Dr John C. S. Breitner MD MPH
Director GRECC (S-182)
VA Puget Sound Health Care System
1660 So. Columbian Way
Seattle, WA 98108, USA
jcsb@u.washington.edu

Professor Christopher J Bulpitt MBBS MD
FRCP
Professor of Geriatric Medicine
Imperial College London
Faculty of Medicine, Care of the Elderly,
Hammersmith Campus
Du Cane Road, London. W12 0NN
c.bulpitt@imperial.ac.uk

Dr Barry R. Davis MD PhD
University of Texas-Houston Health
Science Centre
School of Public Health
1200 Herman Pressler St, Suite E801,
Houston, TX 77030
bdavis@sph.uth.tmc.edu

Professor Robert G. Hart MD
Professor of Medicine (Neurology)
University of Texas Health Science Centre
7703 Floyd Curl Drive, MC 7883
San Antonio, Texas USA 78229-3900
hartr@uthscsa.edu

Professor Charles H. Hennekens BS MD
MPH MS DrPH DSc
Research Professor
Department of Biomedical Science,
Centre of Excellence,
Florida Atlantic University (FAU)
Boca Raton, FL 33432, USA
PROFCHHMD@prodigy.net

Dr Christophe Tzourio
INSERM U360, Hôpital de la Salpêtrière &
Neurology Department, Hôpital Lariboisière
Paris, FRANCE
christophe.tzourio@chups.jussieu.fr

GENERAL PRACTICE ADVISORY COMMITTEE

Professor Justin Beilby
Head
Department of General Practice
Adelaide University
Adelaide 5005 SA
justin.beilby@adelaide.edu.au

Professor Jonathan Emery
Professor of General Practice
Discipline of General Practice
University of Western Australia
Claremont, 6010 WA
jemery@meddent.uwa.edu.au

Professor Claire Jackson
Head
Department of General Practice
Discipline of General Practice
University of Queensland
Herston, 4029 QLD
C.Jackson@uq.edu.au

Professor Michael Kidd
Head
Discipline of General Practice
The University of Sydney
Sydney, NSW
michael@gp.med.usyd.edu.au

Professor Mark R Nelson
Chair of Discipline of General Practice
School of Medicine
University of Tasmania
Hobart, Tasmania 7001
Mark.Nelson@utas.edu.au

Professor Leon Piterman
Head
Department of General Practice
Monash University
East Bentleigh, VIC
leon.piterman@med.monash.edu.au

Dr Nigel Stocks
Acting Head
Department of General Practice,
University of Adelaide
Adelaide, 5005 SA
nigel.stocks@adelaide.edu.au

Professor Marjan Kljakovic
Head
Academic Unit of GP and Community
Health, Medical School
Frank Fenner Building 42
ANU, Canberra ACT 0200
Marjan.kljakovic@anu.edu.au

ENDPOINT ADJUDICATION COMMITTEE (EAC)

Professor Francis Dudley MD FRACP
Head
Department of Gastroenterology
Alfred Hospital
Commercial Rd
PRAHRAN 3181
AUSTRALIA
fdudley@alfred.org.au

Professor Graham Giles BSc MSc PhD
Cancer Epidemiology Centre
The Cancer Council Victoria
1 Rathdowne Street
Carlton Vic 3053
Australia
Graham.Giles@cancervic.org.au

Professor Trefor Morgan MD FRACP
Department of Physiology
University of Melbourne
AUSTRALIA
treforom@unimelb.edu.au

Professor Elsdon Storey MBBS D.Phil
FRACP
Professor of Neuroscience and Director,
Department of Neurosciences and Van
Cleeef Roet Centre for Nervous Disease,
Department of Medicine
Monash University
Pahran 3181
elsdon.storey@med.monash.edu.au

Professor Geoffrey A Donnan MBBS MD
FRACP
Director, National Stroke Research Institute
Austin & Repatriation Medical Centre
Level 1, Neurosciences Building
Gate 10, Banksia Street
Heidelberg West Vic 3081
gdonnan@unimelb.edu.au

DATA SAFETY AND MONITORING BOARD (DSMB)

Chair

Prof Lindon MH Wing MBBS FRACP
Dean
School of Medicine
Faculty of Health Sciences
Flinders University of South Australia
Bedford Park,
South Australia 5001
deansom@flinders.edu.au

Professor Graeme Hankey
Department of Medicine
University of Western Australia
Royal Perth Hospital
Wellington Street
Perth Western Australia 6000
gjhankey@cyllene.uwa.edu.au

Assoc Prof Philip Ryan, MBBS FAFPHM
Department of Public Health,
University of Adelaide
North Terrace, Adelaide 5005
philip.ryan@adelaide.edu.au

Professor Charles H. Hennekens BS MD
MPH MS DrPH DSc
Research Professor
Department of Biomedical Science
Centre of Excellence
Florida Atlantic University (FAU)
Boca Raton, FL 33432, USA
PROFCHHMD@prodigy.net