A study of the long term effects of aspirin and other factors on the health of older persons

Protocol
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1. INTRODUCTION

1.1 Summary
ASPREE-XT is a post-treatment, longitudinal observational follow-up study of ASPREE participants [ASPREE Investigator Group, 2013; www.aspree.org; McNeil et al 2017].

1.2 ASPREE Background
ASPREE (ASpirin in Reducing Events in the Elderly) is a joint US/Australian research project that determined whether low-dose aspirin increases healthy life-span, defined as survival free of dementia and disability. ASPREE began in 2010 and completed recruitment in 2014. It was a randomized, double-blind, placebo-controlled, primary prevention trial of daily 100 mg of aspirin in a population of healthy older people in the United States (US) and Australia with a median period of treatment of 4.7 years. ASPREE’s primary outcome was length of survival free of dementia and disability and had secondary outcomes encompassing the major health issues related to aging. The trial involving 19,114 persons aged 70 and above (65 years and above for US minorities) is distinctive for its large size, methodological rigor and high participant retention rate in both countries.

ASPREE was unique in the following aspects:

1. It was the first large scale trial to incorporate dementia-free and disability-free survival as a primary outcome. This is now recognized as an appropriate goal of treatment in a primary prevention population of this age group. Within a clinical trial context disability-free survival incorporates an estimate of the overall benefits and risks of aspirin in a single outcome measure.

2. It was one of the first primary prevention trials of aspirin to include cancer incidence, metastases or mortality as a pre-specified endpoint. Recent meta-analyses [Rothwell et al. 2010, 2011, 2012] suggests that aspirin has a significant chemopreventive effect becoming evident after a period of 4+ years of aspirin treatment, but questions remain about the magnitude of benefit, and whether it applies to treatment of all cancers and to older people.

3. It did provide information about the impact of aspirin on a range of other conditions (e.g. dementia, CVD, stroke, depression, bleeding) where aspirin has been claimed to have benefit (or risks).
The intervention phase of the trial ended in June 2017 after the NIA determined that it was highly unlikely that aspirin would show a benefit on the overall primary outcome within the planned 5-year time frame. The primary results of the study were published as three manuscripts in the New England Journal of Medicine in September 2018 [McNeil et al. 2018a; McNeil et al. 2018b; McNeil et al. 2018c].

1.3 ASPREE Strengths

For a study involving elderly participants, ASPREE achieved high retention rates and maintained a very high standard of data quality. After a median of 4.7 years of follow up, the percentage of participants who:

- have withdrawn (1.2%) or are out of contact for more than 6 months (2.4%) are very low;
- are still alive (5.4% are deceased) and not withdrawn or lost to follow up, continue to attend annual visits (90%), have phone call annual visits (3%) and have agreed to allow us to continue tracking their medical records without other regular contact (7%).

Apart from the large size of the cohort and very low loss to follow-up, other strengths include a high level of clinical documentation, biospecimens collected at two time points in Australia, and at year three in the United States and that all key outcomes are adjudicated by panels of specialist clinicians.

Enthusiasm from the participants themselves to continue is high, based on their response to a question asked in 2017 about continuing with the study in some form; >95% of respondents in Australia said “yes” to this question.

1.4 Cessation of ASPREE trial medication

ASPREE outcomes were closely followed by a Data and Safety Monitoring Board (DSMB) and the National Institute on Aging (NIA). On reviewing the most recent data, the NIA observed very little difference between the groups taking aspirin or placebo, in length of life free of dementia and disability since the start of the study treatment. The NIA concluded that, after more than 80,000 person years of follow-up had accrued (close to the original number planned for ASPREE), it is extremely unlikely that the study would show a benefit for this, the main study outcome, even if participants continued to take study medication through to the
end of December 2017 as originally planned.

Taking this into account, the NIA determined that ASPREE participants be advised to stop taking their study medication, via letters sent in the middle of June 2017.

Although the trial medication was ceased, the study activity was not stopped and ASPREE participants continued with scheduled visits and phone calls through 2017. An observational follow-up phase, that will be known as ASPREE-XT, began in January 2018. This enables the monitoring of possible delayed effects of aspirin treatment, primarily on cancer incidence, metastases and mortality.

Continuity of contact with study participants is the key to retention of the cohort for any ongoing or future studies.

2. ASPREE-XT (ASPREE-eXTension)

2.1 Aspirin and Cancer Prevention

The ability of ASPREE to answer outstanding questions about aspirin’s effect on malignancy provides a strong rationale to follow the ASPREE participants for a further 5+ years. Current evidence suggests that low-dose aspirin may delay the onset of certain malignancies and reduce metastatic spread. However, these chemopreventive effects do not become apparent until after 4-5 years of continuous aspirin therapy [Rothwell et al. 2010, 2011, 2012]. Additionally, evidence suggests that the chemotherapeutic effect of aspirin may be dependent on the type, and even subtype, of cancer.

ASPREE has prospectively collected data on cancer incidence throughout the trial using histological and specialist verification to ensure accurate classification, including cancer subtype, but longer term data collection is needed to quantify the potential magnitude of this effect and to define those cancer subtypes with the greatest benefit. These data have significant public health implications, given the increasing incorporation of aspirin into guidelines for the chemoprevention of colorectal cancer in the general population. With NCI’s support, cancer tissue and blood samples for genomic and other analyses have been biobanked; resources that will contribute to understanding of the biological effects of aspirin that might explain this action. The ability to confirm and investigate this delayed effect of aspirin on malignancy requires that the full ASPREE cohort continue to be followed with
minimal attrition.

In addition to monitoring the incidence of malignancy within the ASPREE cohort, the opportunity will be taken to observe any other residual effects of aspirin on the endpoints being monitored in the cohort.

2.2 ASPREE Population as the basis for longitudinal aging cohort

As ASPREE participants have been followed within the context of a clinical trial, the study has a high degree of rigor that provides several unique advantages as the basis of a longitudinal cohort study of aging. These include:

1. Absence of dementia at baseline (defined by a 3MS score of >77)
2. Detailed cognitive measures on all participants every 2 years
3. Dementia outcomes adjudicated in all cases
4. Other key health areas including cancer, cardiovascular disease, cerebrovascular disease, frailty, depression and significant bleeding, are adjudicated by expert committees or measured during face-to-face contact
5. Very low loss-to-follow-up (<1%)
6. Extensive medical information & data about personal, environmental & genomic predictors
7. Baseline (12,228) & 3 year (>11,500) bloods allowing for the assessment of novel biomarkers

The ASPREE cohort therefore provides a large and unique cohort of elderly individuals where cognitive function has been monitored intensively as well as most other key areas of medical significance. Coupled with the availability of clinical and genomic information, the cohort provides a unique opportunity to study cognition and other major conditions of aging.

2.3 Funding for ASPREE-XT

In 2016, Australia was awarded funds from the National Health and Medical Research Council (NHMRC) through the competitive grants process to fund ongoing contact with ASPREE participants in Australia through 6-month phone calls, to track colorectal cancer events through electronic health records and to collect samples of colorectal cancer tissue. This funding is from 2017-2021, forming the basis for ASPREE-XT.
For the years of 2018-2019, NIH (NIA and NCI) supplied bridge funding to continue study activity, including face-to-face contact and phone calls in the US and Australia.. At the invitation of the NIA, the ASPREE investigators submitted a grant application to the NIH seeking funds to continue the follow-up of the ASPREE cohort past the bridge funding in 2018. Funds have since been awarded by the NIH to enable the ASPREE investigators to maintain the cohort and allow the study of multiple aging outcomes for a further five years (2019 - 2024) (see Table 1 below for details).

2.4 **Study Aims**

ASPREE participants will be followed for a longitudinal, observational follow-up study after the treatment phase to determine:

1. Long term effects of daily aspirin treatment on the incidence of cancer, metastases and cancer-associated mortality.
2. Long term effects of daily aspirin treatment on the ASPREE secondary outcomes including cognitive decline and frailty.
3. Effects of aspirin cessation on the ASPREE cardiovascular outcomes.
4. Demographic, comorbid, genomic and environmental factors that contribute to the maintenance of cognition and other aspects of healthy aging in a highly phenotyped cohort of older adults.

2.5 **Study Population**

The characteristics of the ASPREE participants at the time they were randomized into ASPREE are described in [McNeil et al. 2017].

3. **ASPREE-XT STUDY DESIGN**

ASPREE-XT is a longitudinal, observational follow-on study of ASPREE participants.

The methodology of ASPREE-XT is based closely on ASPREE [ASPREE investigator group, 2013; www.aspree.org; McNeil et al. 2017]. Clinical, neurocognitive and physical function measurements, questionnaires for mood, quality of life, physical ability and collection of personal health, demographic and lifestyle details are the same in ASPREE-XT as those conducted and described for ASPREE.
Since ASPREE-XT is an observational study, the endpoints for ASPREE will be collected and adjudicated in a similar way for ASPREE–XT but will be referred to as ASPREE-XT Outcomes. These will not be divided into primary and secondary endpoints.

In 2018, participants were invited to enroll in ASPREE-XT. At the first ASPREE-XT study visit, or via mail, they were provided with an information sheet and consent form for the study (Table 1). Participants who wish to only be contacted by phone were provided with information and a consent form by mail with health and other study data collected by phone call.

<table>
<thead>
<tr>
<th>Year</th>
<th>2017</th>
<th>Bridging year (2018)</th>
<th>ASPREE-XT (2019 and beyond)</th>
</tr>
</thead>
</table>
| All ASPREE participants are eligible for ASPREE-XT | ASPREE Close-out visits | • Consent to ASPREE-XT  
• Face to face Annual visit for ASPREE-XT or phone call for data collection  
• 6 month phone calls for data collection  
• Medical records collection  
• Endpoint tracking  
• Samples of cancer tissue | • Face to face Annual visit for ASPREE-XT or phone call for data collection  
• 6 month phone calls for data collection  
• Medical records collection  
• Endpoint tracking  
• Samples of cancer tissue |

Table 1. Timeline for ASPREE participants willing to continue with ASPREE-XT. Annual face-to-face visits and 6 month phone calls will continue beyond 2018, following the securing of additional NIH funds. Phone calls, cancer medical records and cancer tissue collection are funded separately in Australia from the NHMRC until 2021.

3.1 Recruitment

In Australia, ASPREE participants who were attending study visits in 2017 were invited by phone to attend an ASPREE-XT study visit which was at their local GP clinic, community venue or study site. In advance of the appointment, the PICF and some of the ASPREE-XT questionnaires (the LIFE questionnaire, clinical event details, SF-12, cancer screening information, aspirin / smoking / alcohol use, pre-populated participant and nominated contact(s) details for confirmation), were sent by mail to the participant, with a request to bring the completed paperwork along to the study visit. All ASPREE-XT participants will be very familiar with these questionnaires from ASPREE.
ASPREE participants who had chosen to receive study phone calls only in 2017 were sent an
invitation to participate in ASPREE-XT, along with a PICF and the questionnaires listed above,
with a reply paid envelope. Approximately two weeks later, the participant was contacted to
conduct the study visit by phone, including whether the person is willing to participate in
ASPREE-XT and a reminder to return the completed PICF if they haven’t already done so. In
the US, once a site had IRB approval for ASPREE-XT and consenting documents, the ASPREE
randomized participants were 1) mailed an ASPREE-XT consent form or addendum to sign
and return. Once the signed consent was received by site staff, an ASPREE-XT in-person visit
or phone call or medical record review was scheduled, based on the participant’s desired
follow-up status and their ASPREE visit window. Follow-up of consent documents mailed but
not returned was monitored by the sites. 2) invited to an in-person ASPREE-XT consenting
visit that could also include annual visit activity depending on their ASPREE visit window, or
schedule the visit activity for a separate date due to a later ASPREE visit window. In advance
of the visit, the consent and some of the ASPREE-XT questionnaires (the LIFE questionnaire,
clinical event details, SF-12, cancer screening information, aspirin / smoking / alcohol use),
may be sent by mail to the participant with a request to bring the completed paperwork along
to the study visit.

Waiver of consent – Deceased participants

In Australia, a waiver of consent applies to the small sub-group of ASPREE participants who
have died since the end of the intervention phase of ASPREE (12 June 2017), and who never
had the opportunity to consent to ASPREE-XT. This waiver of consent will allow the ASPREE
investigators to access relevant medical records of the participants in question, to obtain
supporting documentation that will assist in determining underlying cause of death, and to
identify other clinical events of relevance to the study that occurred around the time of the
participant’s death.

4. OBJECTIVES

The primary objective is to determine whether there are long-lasting effects of an average of
4.7 years of treatment with daily low-dose aspirin on the key outcome measures of cancer,
metastases and cancer mortality.

An additional objective is to study the impact of demographic, comorbid, environmental and
genomic factors on the maintenance of cognition and other aspects of health amongst the
elderly. This objective will enable insights that may improve advice available to US and Australian adults to maintain health during their later years.

5. STUDY OUTCOMES

5.1 Main Outcomes

- Death or dementia or persistent physical disability (this composite was the primary endpoint for ASPREE)
- All-cause mortality
- Fatal and non-fatal cancer, excluding non-melanoma skin cancer, and metastases
- Dementia - diagnosed based on DSM-IV criteria
- Physical disability - defined as a confirmed, and persisting for at least 6 months, self-report or appropriate proxy report of ‘a lot of difficulty’, or ‘inability to perform independently’ any one of the 6 Katz basic Activities of Daily Living (ADLs) [Katz & Apkon 1976].
- Mild Cognitive Impairment (MCI; assessed using the Modified Mini-Mental State Examination or 3MS [Teng et al. 1987] and other cognitive function measures – see below)
- 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 hospitalization for heart failure
- Depression; assessed using the CES-D (Center for Epidemiologic Studies – Depression) -10 [Radloff, 1977] questionnaire, or hospitalization for depression
- Major hemorrhagic events
- Frailty [Fried et al. 2001]

Note: The terms ‘outcome’ (ASPREE-XT) and ‘endpoint’ (ASPREE) will be used interchangeably in this Protocol.

Each of the endpoints has objective ascertainment criteria (outlined in Appendix 1) and each will be reviewed by the Endpoint Adjudication Committee (EAC). The cancer, cardiovascular and cerebrovascular endpoints represent the major expected causes of mortality in the study population, whilst dementia, cognitive decline, physical disability and depression impact on the individuals’ ability to participate in healthy active life. Hemorrhage is an important endpoint.
contributing to the evaluation of the risk versus benefits post-aspirin therapy in this population. This endpoint process is based on the ASPREE methodology for endpoint ascertainment.

5.2 Other non-adjudicated outcomes

- Physical function measures: performance-based (including gait speed and hand grip tests) and self-reported (LIFE questionnaire [Pahor et al. 2006])
- Additional cognitive function measures: Symbol-Digit Modalities Test (SDMT) [Smith, 1982], Hopkins Verbal Learning Test – Revised (HVLT-R) [Shapiro et al. 1999], Controlled Oral Word Association Test (COWAT) [Ross, 2003], and Color Trails [D'Elia, 1996]
- Quality of life (Short Form – 12 or SF-12 [Ware et al. 1996])
- Full blood examination results (Australia) / Complete blood count (US); including hemoglobin
- Non-fasting plasma/serum creatinine (for eGFR) and glycosylated hemoglobin (HbA1c)
- Urine albumin:creatinine ratio for the detection of microalbuminuria
- Hospitalization and clinical events of aging

5.3 Outcome Ascertainment

At each annual visit or call, and 6 month 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 outcome will trigger the collection of information for event confirmation and adjudication by the EAC. All such events will be recorded on electronic Case Report Forms (eCRF). Confirmation of endpoints will be ascertained by collecting information from the following sources:

- Details from medical records from the usual treating physician or practice–held medical record
- Medical records from other treating specialist physicians or secondary/tertiary medical care centers
- eCRFs containing standardized questionnaires for the assessment of cognitive function, physical function and quality of life
• In Australia, hospital records/discharge summaries, pathology reports, Medicare (MBS) and Pharmaceutical Benefits Scheme (PBS) records, aged care data sets held by the Australian Institute of Health and Welfare (AIHW), National Death Index (NDI), cancer and other registries, Government databases containing information on health and/or vital status. In the United States, hospital records/discharge summaries, pathology reports, public health records, Medicare data, the National Death Index (NDI), and other government databases will be used to obtain health information and/or vital status.

6. STUDY COHORT

ASPREE randomized a total 19,114 participants, 16,703 in Australia and 2,411 in the USA. Overall, 56% of randomized participants are female (10,778) and 9% are minorities (1,670). The co-morbidity profile of both Australian and USA participants indicated that the ASPREE population was somewhat healthier than the general population in both countries at baseline, as expected given the eligibility criteria. A summary of the baseline characteristics of the ASPREE participants is reported in the paper [McNeil et al. 2017].

6.1 Inclusion criteria
• Randomized participants of the ASPREE study in Australia or the US
• Willing and able to provide informed consent and willing to accept the study requirements, or
• Willing to allow a surrogate or legally authorized representative to provide informed consent

6.2 Exclusion criteria
• Inability or unwillingness to provide informed consent or surrogate / legally authorized representative’s consent.

6.3 Participant discontinuation
A participant is free to withdraw from ASPREE-XT at any time. If a participant withdraws from the study altogether (i.e. from attending annual visits or follow-up through medical records) or is removed from the study for any reason, this will be recorded in the database.
7. MEASUREMENTS AND DATA MANAGEMENT

7.1 Schedule of study visits

ASPREE-XT measurement and study activity schedule for the bridging period (2018), and 2019 and beyond, is summarized in Table 2.

Table 2. ASPREE-XT Measurement and Study Activity Schedule

<table>
<thead>
<tr>
<th>Measurement/ Activity</th>
<th>2018</th>
<th>2019 and beyond</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Annual Visit (XT01)</td>
<td>6 month Call</td>
</tr>
<tr>
<td>Obtain informed consent (or updated consent, if required)</td>
<td>X^a</td>
<td>X^ab</td>
</tr>
<tr>
<td>Concomitant medications</td>
<td>X^a</td>
<td></td>
</tr>
<tr>
<td>Aspirin use</td>
<td>X^a</td>
<td>X^b</td>
</tr>
<tr>
<td>Demographics, &amp; lifestyle factors^a</td>
<td>X^a</td>
<td></td>
</tr>
<tr>
<td>Family &amp; personal medical history (including cancer)^a; cancer screening^a</td>
<td>X^a</td>
<td></td>
</tr>
<tr>
<td>Blood pressure &amp; heart rate, body weight</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Quality of Life</td>
<td>X^a</td>
<td></td>
</tr>
<tr>
<td>- SF-12^a</td>
<td>X^a</td>
<td></td>
</tr>
<tr>
<td>Assess cognitive function &amp; depression - 3MS; CES-D-10</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Additional cognitive function assessments (XT02 onwards)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>- COWAT, SDMT, HVLT-R, Color Trails</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Assess physical disability</strong></td>
<td>X^a</td>
<td>X^b</td>
</tr>
<tr>
<td>- KATZ ADLs^ab &amp; LIFE questionnaire^a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assess physical function</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>- Walk test and grip strength</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical event reporting</td>
<td>X^a</td>
<td>X^b</td>
</tr>
<tr>
<td>- Questionnaire^ab &amp; medical record review</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory measures (XT01 only)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>- Hb, Plasma/Serum Cr &amp; Glucose, uACR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory measures (XT02 onwards)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>- Plasma/Serum Cr; HbA1c; Full Blood Examination (FBE) (Aus) / Complete Blood Count (CBC) (US), including Hb; uACR</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>
### Endpoint documents collected

<table>
<thead>
<tr>
<th>Endpoint documents collected</th>
<th>E</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer tissue sample collection</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Saliva collection</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>

X indicates that all measures are carried out except where superscripts \(^a\) indicates those tests and/or consent forms that may be mailed ahead of the visit to be then brought to the visit or \(^b\) administered by phone; * alcohol and smoking information; E indicates documents are collected for endpoints at any time there is a trigger; C indicates cancer tissue sample collection which occurs at any time during the year after a cancer endpoint is confirmed; S indicates collection of saliva from participants who have not yet provided a DNA sample during ASPREE but are willing to do so during ASPREE-XT (Aus participants).

**Telephone calls** will take place approximately 6 months after the ASPREE-XT visit for purposes of retention and for clinical event reporting. At the 6 month call, participants will be asked specifically about all endpoints, aspirin use and will be administered the Katz ADL’s.

### 7.2 Proposed study activity and data collection

Measurements and data will be collected by the research staff after the participant has provided informed consent to participate in the study. The information to be collected at a study visit, by phone call or by US. Mail, and includes the following (and outlined in Table 2):

(a) Basic demographic and lifestyle factors including living situation, smoking history and alcohol use

(b) Medical morbidity – medical record review and questionnaire / participant self-reporting.

(c) Participant reported information about screening for cancer (cancer screening details may be obtained also through medical records provided the information clearly states the test was for cancer screening)

(d) Blood pressure and heart rate: measured in the seated position following 5 minutes of rest using an oscillometric device. Two measurements will be taken 1 minute apart

(e) Body weight using electronic scale

(f) Cognitive function and depression: assessed using the 3MS score [Teng et al. 1987] and the CES-D-10 [Radloff, 1977] questionnaires. 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, and also to ascertain new onset depression. Additional cognitive assessments will be administered
at pre-determined intervals from 2019 and beyond, including the COWAT [Ross, 2003], SDMT [Smith, 1982], HVLT-R [Shapirol et al., 1999], and the Color Trails [D’Elia et al., 1996]

(g) Physical disability: assessed by the participant’s self-reported ability, or an appropriate proxy report, 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 [Pahor et al. 2006]. The Katz ADLs are best administered face-to-face although they can be administered over the phone.

(h) Laboratory measures: Referral to a local Pathology Provider (in Australia) or direct collection of a blood sample (~12 ml) and urine spot test (minimum of 20 ml). For 2018, the requested measures were creatinine, glucose, hemoglobin, and urine albumin : creatinine ratio (to detect the presence of microalbuminurea). For 2019 and beyond, an amended set of laboratory measures will be requested (non-fasting blood levels of creatinine, hemoglobin within a full blood examination (FBE) (Aus) or complete blood count (CBC) (US), glycosylated hemoglobin (HbA1c), and urine albumin : creatinine ratio).

(i) Short Form (SF) -12 score [Ware et al. 1996] – self-administered questionnaire for quality of life.

(j) Physical function testing – timed gait speed test for 3m (8ft) [Guralnik et al. 2000] and hand grip strength measured on a grip strength dynamometer [Onder et al. 2002].

(k) Concomitant medications, indication and year commenced – participant self-reporting, medical record review and family physician report. Participants will be asked to bring in all of the medications that they currently use or have recently used, including over-the-counter medications, to verify their current medications.

(l) Clinical event reporting. Throughout the year, medical records documents will be collected to support endpoint processing. Triggers from participants’ self-report in person or by phone will serve as a basis for requesting relevant documents from various sources.

(m) Cancer tissue retrieval. After an adjudication of cancer endpoint is confirmed, study staff in both countries will seek access to a sample of cancer tissue (see Appendix 5).

(n) Saliva collection (Australia only) for DNA sample will continue in ASPREE-XT for those who still wish to provide a sample (see Appendix 5).
7.3 Participant Retention Plan

- Retention will be encouraged by regular phone contact (6 month intervals) between face-to-face visits.

- Contacts details (including at least 2 alternate contacts) will be updated during face-to-face meetings. Additional contacts are used in the situation where a participant’s contact details change without contacting the study center.

- Newsletters will be sent to family physician co-investigators in AUS and all participants on a regular basis (~2-4 per year) detailing study progress.

If a participant is ‘lost to follow-up’ despite measures detailed above, the following steps will be undertaken:

- Tracking through third party contacts. Details for up to three additional contacts, who do not reside at the same address as the participant, will be updated during ASPREE-XT.

- Crosschecking with morbidity and mortality registries. In Australia, this may include, but is not limited to, linkage of ‘lost to contact’ participants with aged care data sets and with the NDI held by AIHW, with other health data sets held by AIHW, and/or other Commonwealth-based or state-based databases and registries containing vital status or health information. In the United States, the National Death Index (NDI) and Medicare data will be used to ascertain mortality status.

- Data linkage through Medicare numbers will provide updated medical information and clinical events in both countries.

- In Australia, the research staff member will be able to also audit practice and hospital records in the event a participant is unable to be contacted.

7.4 Clinical results of significance

An average blood pressure measurement that is higher than 180/105 mmHg, irregular pulse, low 3MS or high CES-D-10 result detected during a study visit will trigger a notification to the participant’s GP in Australia and will be provided to the participant’s regular treating physician (PCP) in the US if allowed by the participant, who will provide contact details. All pathology results are automatically sent to the participant’s nominated GP in Australia who maintains
clinical oversight of the participant.

7.5 Data quality control

The ASPREE-XT quality assurance plan is based on that prepared for ASPREE and has been designed to ensure that (a) study staff are fully trained and their performance monitored, (b) there is full compliance with the study protocol and ethical requirements, (c) data collected is complete and accurate, and (d) other procedures (e.g. data backup and record storage) are being conducted in accordance with study requirements.

All staff assigned to ASPREE-XT will be provided training covering good research practice, clinical research ethics and procedures. These procedures will be shared in the form of Standard Operating Procedures (SOPs) that will describe, in detail, descriptions of all study procedures. In addition, study CRF’s will be required for completion for each visit. All of these materials will be made available via the AWARD-XT website. Ongoing training will occur in each country and will be coordinated by each respective Coordinating Center. Trial personnel in supervisory positions will be involved with the training to ensure consistency of procedures between staff in both countries. Ongoing competency will be monitored regarding the various cognitive testing that will be administered by site staff. A ‘certification’ process will be in place to maintain a high level of testing quality.

The Data Management Centre (DMC) will be responsible for data editing that will include checks for missing data and inconsistencies. Site staff will be responsible for completing data edits within a reasonable period of time. The DMC will track quality control measures in a quality control report that will be reviewed by the International Data Management Committee and the International Steering Committee on a regular basis. Such measures will include, but are not limited to, number of participants with missed visits, proportion of study participants retained in the study, documentation for reported study events, proportion of participants with laboratory measures, and deviations from the protocol. If issues with data quality are identified for a particular site or sites, corrective action steps based on remote and/or in-person monitoring will be implemented.

7.6 Data Analysis

The observational ASPREE-XT study will be analyzed by statisticians based at the ASPREE Data Management Center, Department of Epidemiology and Preventive Medicine, Monash University, and the Chronic Disease Research Group at Hennepin County Medical Center, part of the Minneapolis Medical Research Foundation.
For ASPREE-XT study outcomes that are in the form of time-to-event, for example cancer incidence and all-cause mortality, groups of participants will be compared using Cox proportional hazards regression with adjustment for appropriate factors that may have confounding effects. The exception to this will be the analysis of randomized ASPREE treatment which will be analyzed in a univariate model to directly compare event rates between the original treatment groups. ASPREE-XT study outcomes that are measured on repeat study visits, for example, cognitive function and SF-12 quality of life, will be analyzed using mixed effect linear models.

7.7 Dissemination and implementation of results

Objectives are:

a) To increase awareness of the ASPREE-XT observational study by disseminating results via repeated messages through scientific and professional channels.

b) To provide physicians, physician’s assistants, practice nurses and nurse practitioners with cues to action via distribution of office posters, prescription cards, and other educational materials.

c) To provide study results and any recommendations arising from the study to the professional and scientific community, as well as the public. This will be achieved through a designated web site that will have the following uploaded: published journal articles, newsletters, presentations, frequently asked questions section, links to other appropriate web sites and downloadable information for personal devices.

8. ADHERENCE TO ETHICAL, REGULATORY AND ADMINISTRATIVE CONSIDERATIONS

8.1 Ethical Considerations

General

This study will be conducted in accordance with the Declaration of Helsinki 1964 as revised in Edinburgh in 2000, and with the National Health & Medical Research Council Guidelines on Human Experimentation.

In Australia, the Alfred Hospital Ethics Committee (ethics #HREC/17/Alfred/198) oversees the ASPREE-XT project as the primary site approver. The project has also been approved by the following secondary ethics committees: the Human Research Ethics Committee (Tasmania)
Network (ethics #H0017149); Monash University Human Research Ethics Committee (ethics #12771); and ACT Health Human Research Ethics Committee (Canberra) (ethics #ETH.3.18.037E) and The University of Adelaide Human Research Ethics Committee (ethics #32802), which accept Alfred Hospital Ethics Committee’s approval via the National Mutual Acceptance Scheme. Each of these ethics committees previously approved the ASPREE study. These committees will be responsible for ethical oversight of the ASPREE-XT at each of the main hubs.

In the US, based on new National Institute of Health Requirements for multi-site clinical trials, the ASPREE-XT study will use a Single IRB of record.

**Information for Participants**

Before obtaining consent, the participant, or appointed surrogate, must be informed of the objectives, any benefits or risks, and requirements of the study. Enrolment in ASPREE-XT is only available to ASPREE participants. This means that all ASPREE-XT participants will be already familiar with the planned study measurements and data collection.

### 8.2 Regulatory Considerations

**Financing**

ASPREE-XT has received funding from the National Institute on Aging and the National Cancer Institute (within the US National Institutes of Health) and the National Health and Medical Research Council (Australia).

**Disclosure of Conflict of Interest**

Full disclosure by all of the key members of the study of their, and their immediate family's, financial relationships with all pharmaceutical and biomedical companies judged to have an active or potential interest in the conduct and outcome of the study will be made annually. Details and conditions of this disclosure are included in Appendix 3.

### 8.3 Administrative Organization

**Individual and Committee responsibilities**

The ASPREE-XT International Steering Committee will be responsible for the overall management and conduct of ASPREE-XT including finalizing the protocol, and approving the operational plan for the study. The committee will be chaired by either the US or AUS Principal Investigator or nominee, on an annual rotation as Chair. The committee will consist of the Co-Chairs, members of the International Operations Committee (see below), Principal
Investigators from sites in the US and recruiting hubs in Australia, plus individuals with special content expertise who may be invited to join. The International Steering Committee will have conference calls as needed, but at least every 6 months.

*International Executive Committee* (IEC) is a smaller committee derived from the International Steering Committee. It will consist of the Co-Chairs of the International Steering Committee, two representatives from the US Operations Committee, two representatives from the Australian Operations Committee and the Chair or Co-Chair of the International Data Management Committee. The IEC will meet by teleconference, as needed. This smaller committee must be prepared to meet at short notice if any urgent issues related to the study should arise.

*National Operations Committees* will be maintained in both countries. Each committee will be responsible for implementing the study, monitoring the progress and ensuring adherence and standardization throughout the study in that country. Each committee will also work to ensure co-ordination, consistency, transfer of data to the Data Management Center and quality control. They will ensure quality control review of laboratory data, clinical measurements and data collection, completeness and entry times of data, site monitoring and source documentation. Each committee will communicate regularly with each other (4-6 teleconferences per year) to ensure consistency of protocol implementation across countries. These Committees may consist of site Principal Investigators or Project Managers and key research personnel and will report directly to the International Steering Committee.

*International Data Management Committee*: This committee will meet monthly in order to monitor the establishment and implementation of the ASPREE Data Management System, the reporting activities and to review all quality assurance reports for the study. The IDMC Chair or Co-Chair will report to the International Steering Committee of ASPREE-XT on Data Management Issues associated with the study.

*Observational Study Monitoring Board (OSMB)*: This committee will be appointed by the NIA and will adhere to the OSMB Charter. The responsibilities and operational details of the OSMB are described in Appendix 4.

The OSMB will be provided with data every 6 months or as requested. The OSMB will meet every 6 months, by teleconference or in-person, to review study progress, data quality control, address policy issues and review total mortality data, adverse events, all safety data and monitor the study progress and data quality. The OSMB will provide a follow-up report and recommendations to the NIA. The OSMB has expertise related to the conduct of clinical trials.
per se and in the primary care sector, epidemiology, biostatistics, clinical pharmacology, geriatricians, and cardiovascular disease. Confidentiality will be maintained during all phases of the trial including monitoring, preparation of study results, review, and response to monitoring recommendations.

**Endpoint Adjudication Committee:** This committee will evaluate individual outcomes blinded to the former randomized ASPREE treatment. Each endpoint will be validated through examination of relevant clinical information. Specialist sub-committees will be appointed, such as the Dementia Adjudication Panel, to adjudicate on specific endpoints with a nominated person as member of the EAC.

**Publications, Presentations and Ancillary Studies Committee:** This committee will be responsible for implementation of the publication policy (see below), coordination of topics and requests for publication, approval for abstracts and submission to conferences, and receipt of proposals for ancillary studies (see below).

**Publication policy**

This policy covers all publications and abstracts originating from ASPREE-XT and any sub-study.

**Authorship** - Manuscripts and abstracts relating to the ASPREE-XT study must include all current members of the International Steering Committee (ISC) using the following formula:

- All publications will be on behalf of ‘the ASPREE-XT 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-XT Study Group in each manuscript
- All clinical site investigators and committee members will be listed on the ASPREE-XT web-site and acknowledged in every publication.
Non-ISC authors utilize the same formula. Disputes about authorship must be notified to the Principal Investigator(s) to be resolved at the next ISC meeting.

*Drafts* - Initial and major upgraded manuscripts and abstracts must be circulated to all members of the ISC and any other Committee within ASPREE-XT when appropriate. Members will have a time limit, typically a maximum of one week, to send responses.

**Ancillary studies**
Ancillary studies must be submitted to and approved by the ISC. 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 ISC and submitted by a Principal Investigator with a maximum of a five page summary of the rationale and method and must include a budget and evidence of funding or a strategy for securing said. The ISC must ensure that any ancillary study will not compromise the main study.
9. REFERENCES


Shapirol AM, Benedict RHB, Schretlen D, *et al.* Construct and Concurrent Validity of the


APPENDIX 1. ENDPOINTS AND OTHER MEASURES

It is important to note that participants in ASPREE-XT are familiar with all tests, assessments and measures proposed. Data collection for ASPREE-XT is the same as for ASPREE except 3 cognitive assessments have been omitted for the first year of visit activity (2018) due to time constraints. These cognitive assessments will be reintroduced in subsequent years, as needed, along with an additional cognitive assessment (the Color Trails).

Endpoint ascertainment in ASPREE-XT, triggers or reports of events, source documentation to support the case, presentation of cases to the EACs and the criteria / decision rules, used by the EACs, will all be the same as for ASPREE. Unless described under each listed outcome, details of the Endpoint ascertainment procedures for each of the following outcomes are provided at www.aspree.org in the ASPREE Protocol.

1. **Main Outcomes**

1.1 Composite ASPREE primary outcome

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

These categories of disability are defined, respectively, as a) all-cause mortality, b) the assessment of dementia by DSM-IV criteria or c) the onset of ‘a lot of difficulty’ or ‘inability’ to perform independently, any one of 6 Katz ADLs.

1.2 All-cause mortality

Death certification and post mortem report. In the absence of a death certificate or post mortem report, hospital or GP records describing the death will be used. National Death Index searches will be conducted in both countries. In Australia, an on-line database (Ryerson Index) will be regularly accessed for information regarding deaths and funeral notices and matched to the ASPREE-XT participants.

1.3 Incidence of fatal and non-fatal cancer (excluding non-melanoma skin cancer) including metastases

1.4 Incidence of all-cause dementia

1.5 Loss of physical ability for activities of daily living

1.6 Fatal and non-fatal cardiovascular events

1.7 Mild cognitive impairment

1.8 Physical ADL disability

1.9 Depression

1.10 Major hemorrhagic events - *Clinically significant bleeding*

2. **Other non-adjudicated measures**

2.1 Physical Performance
a) Performance based measures  
b) Self- (or proxy-) reported measures (using ADL and IADL Questionnaires)  
c) Frailty measures  

2.2 Quality of life  

2.3 Glycosylated hemoglobin (HbA1c), and non-glycosylated hemoglobin (Hb) within a full blood examination (FBE) (Aus) or complete blood count (CBC) (US)  

2.4 Plasma creatinine (eGFR) and Urine Albumin:Creatinine Ratio  

2.5 Hospitalizations and clinical events of aging  

APPENDIX 2. SAMPLE SIZE & STUDY CALCULATIONS  
All living ASPREE participants, who have not withdrawn from ASPREE, are eligible for ASPREE-XT. In Australia, this number is expected to be approximately 14,000 people. In the US, this number is expected to be approximately 1,500 people.  
For ASPREE-XT study outcomes that are in the form of time-to-event, for example cancer incidence and all-cause mortality, groups of participants will be compared using Cox proportional hazards regression with adjustment for appropriate factors that may have confounding effects. The exception to this will be the analysis of randomized ASPREE treatment which will be analyzed in a univariate model to directly compare event rates between the original treatment groups. ASPREE-XT study outcomes that are measured on repeat study visits, for example cognitive function and SF-12 quality of life, will be analyzed using mixed effect linear models.  

APPENDIX 3. CONFLICT OF INTEREST  
1. The ASPREE and ASPREE-XT projects are federally-funded studies from the National Institutes of Health. All recipients of federal funding are required to have their own Financial Conflict of Interest policies. This Conflict of Interest policy is in addition to any institutional Financial Conflict of Interest policies that the recipient adheres to as a recipient of federal funding.  
2. This full policy is to be made public on our Website and in publications when possible.  
3. The primary concerns are twofold. First, that the ASPREE-XT investigators maintain the internal integrity of the study by which we mean the confidence among ourselves (investigators and staff) as we develop and modify the detailed protocol, that advice is being given and decisions are being made in an unbiased and fully informed manner as possible. Second, that we maintain the external integrity of the study by which we mean the acceptance of our process and results as having met public standards of conduct.  
4. To meet these goals we will obtain full disclosure by all of the key members of the study (as defined below in item 4) of their, and their immediate family’s, financial relationships with all pharmaceutical and biomedical companies judged to have an active or potential interest in the conduct and outcome of the longitudinal ASPREE-XT study. These are to be reported annually on a standard form, each of which will be reviewed on at least an
annual basis or more frequently if there is a significant change from the last report, by an Oversight Committee. The Oversight Committee will be comprised of the Chair of the Steering Committee and the Chair of the International Operations Committee. The information to be reported will not include specific dollar amounts, although the definitions below require that certain relationships be segregated by those above and below certain dollar thresholds.

5. All of the study PIs, Co-PIs, and the Steering Committee and its various subcommittees’ members are covered by this policy.

6. A conflict of interest will not necessarily exclude any member of the study from participating in study discussions, unless required in individual cases by the Oversight Committee. However, full disclosure of all potential conflicts of interest will be made at Committee meetings to all attendees in an effective, but non-cumbersome manner. This includes the full Steering Committee as well as each of its sub-committees.

7. A significant financial conflict of interest, defined below, will cause a person to excuse himself or herself from voting on all issues related to the conflict. All such actions will be recorded and kept as part of the study record by the Oversight Committee.

8. All financially relevant relationships are to be reported. Only those relationships that are between the individual and the specific company (rather than between the individual's parent institution and the specific company, for example) present the potential for a significant financial conflict of interest, defined under paragraphs 10a and 10b below. Specifically, research funding for contracts or grants to the parent institution which provide support to the individual, his/her laboratory or his/her close scientific collaborators is not ordinarily judged to present the potential for a financial conflict of interest, although such awards are to be fully disclosed as a part of this policy.

9. Those financially relevant relationships that are to be reported include employment, consultancies, board memberships, honoraria, stock ownership or options, grants, contracts, patents received or pending, and royalties. The Oversight Committee will decide, with #9 below as a guideline, whether any of these and other relationships in each individual case is significant enough to warrant excuse from voting or discussions.

10. A significant financial relationship is defined to exist:

   a) when the dollar amount awarded on an annual basis, or expected-to-be awarded on an annual basis, with regard to each related corporate relationship exceeds $10,000. The Oversight Committee may also judge lower dollar amounts as significant in specific/individual circumstances.

   b) when there is any equity holding in a related company (excluding mutual funds and blind trusts). Again the Oversight Committee may decide in individual circumstances that the equity holdings are relatively minor enough to not present a real conflict of interest.

   c) Significant financial relationships in existence since January, 2018 between ASPREE-XT investigators and all pharmaceutical and biomedical companies, judged to have an active or potential interest in the conduct and outcome of the longitudinal study, will be described in all study reports and publications. In addition, we will meet or exceed the reporting standards of the journals publishing our manuscripts.
APPENDIX 4. OSMB CHARTER

ASPirin in Reducing Events in the Elderly (ASPREE) Follow-up Phase
Observational Study Monitoring Board (OSMB) Charter

Introduction

A seven-member OSMB will act in an advisory capacity to the National Institute on Aging (NIA) to monitor data quality and evaluate the progress of the follow-up phase of the ASPREE study conducted by Dr. Anne Murray of the Berman Center for Outcomes and Clinical Research, Minneapolis, MN and Dr. John McNeil of Monash University, Melbourne, Australia. The follow-up phase started on June 13, 2017 after the ASPREE intervention phase ended. ASPREE intervention phase procedures (other than those related to the intervention) will be maintained until December 2017. A new protocol for the remainder of the follow-up period will be prepared for review by the OSMB before that date.

Responsibilities of the OSMB

- Review and approve the IRB-approved ASPREE follow-up phase protocol and consent documents as well as the Standard Operating Procedures (SOP) prior to protocol initiation. Review and approve any changes to the protocol, consent document templates and SOP during the study.

- Monitor participant safety, protocol adherence, cohort retention, annual visit completion, study medication cessation, participant follow-up status, data completeness, outcome adjudication process and status of data cleaning. Advise NIA if corrective measures are needed.

- Monitor rates of important health events. If there are clinically important differences between study groups, advise NIA on the need for, timing, and mode of dissemination of these findings.

- Review proposed ancillary studies with regard to safety and impact on participant burden, and make recommendations on approval of these studies.

- Upon request by NIA, provide comments to NIA on analyses for major study outcome papers and drafts of these papers.

Communications

To mitigate any potential conflicts of interests, all communications between the investigators and the OSMB members on any issues related to the study shall be held through the NIA Project Officer (PO) or NIA Clinical Trials Operations Support Center (CTOSC) contractor. However, the investigators shall make presentations, discuss the reports, and ask and answer questions during the OSMB meetings and webinars/teleconferences.

Scheduling, Timing, and Conduct of Meetings

The OSMB meetings will be held either in person or via a webinar/teleconference at least two times a year at the call of the Chairperson and/or NIA PO. Meetings and webinars/teleconferences will be scheduled by the study staff or by NIA CTOSC. Four OSMB members will constitute a quorum. The NIA PO and/or NIA Project Scientist will be present at
every meeting. Meetings will be closed to the public because discussions may address confidential participant data. The OSMB meetings will consist of the open session and two optional sessions – Closed and Executive.

- **Open session** will be attended by the OSMB members, NIA, CTOSC and study staff. During the open session, information will be presented to the OSMB by the study and NIA staff, as appropriate, followed by general discussion.
- An optional **Closed session** could be called by the OSMB members or NIA staff prior to or during a meeting. This session will be attended by the OSMB members and NIA and CTOSC staff to discuss any confidential or sensitive issues.
- An optional **Executive session** could be called by any OSMB member prior to or during a meeting and only OSMB will attend this section.

**Meeting Materials**

There will be only the Open Session Report presented to the OSMB, which may direct additions and other modifications to the report on a one-time or continuing basis. The agenda and meeting materials will be provided to the OSMB by NIA PO or CTOSC not later than 10 calendar days prior to the meeting. Accordingly, the investigators shall submit the meeting materials to NIA PO or CTOSC at least 12 calendar days prior to the meeting.

**Reports from the OSMB**

A formal report containing the OSMB’s recommendations will be prepared by NIA or CTOSC staff. Given confidentiality concerns, the report will include recommendations, but no details about the OSMB’s discussion. The draft report will be sent to the OSMB members for review and approval. Once approved by a majority of the OSMB members, the NIA PO will forward the formal OSMB recommendations to the investigators and will indicate whether NIA concurs with the report.

If there are unresolved differences of opinion among OSMB members, reports from the OSMB may consist of majority and minority reports. In these cases, majority and minority are required to approve their respective portions of the report. The report may also include a dissenting opinion by an individual Board member, which will be included as an addendum.

**Confidentiality**

All materials, discussions and proceedings of the OSMB are completely confidential. Members and other participants in OSMB meetings are expected to maintain confidentiality. OSMB members will be required to sign a Non-Disclosure/Confidentiality Agreement and will be required to inform the NIA PO about any new conflicts of interest developing.
APPENDIX 5. CANCER TUMOR TISSUE BANKING

Funding
From 2013-2017, the National Cancer Institute in the US (one of the Institutes within the NIH) funded the ASPREE Cancer Endpoints Study (ACES) as a subsidiary of the main ASPREE study. ACES allows for the exploration of DNA related molecular mechanisms, along with other physiological mechanisms, of aspirin’s protective effect against cancer and cancer-associated mortality and metastases, using tumor tissue. Additionally, the role of aspirin on different cancer subtypes can also be examined. A key component of this study is to establish a biologic specimen repository for tumor tissue from the ASPREE healthy aging population in the US and Australia, for future use by ASPREE, NIA and NCI investigators, and academicians from the broader research community. Participants in the ASPREE-XT longitudinal, observational, follow-up study will be asked to agree to allow ASPREE-XT to be provided with a small specimen of tumor tissue collected at the time of diagnosis or treatment, in those diagnosed with cancer.

In 2016, Australia was awarded funds from the National Health and Medical Research Council (NHMRC) through the competitive grants process to fund ongoing contact with ASPREE participants in Australia through 6-month phone calls, to track colorectal cancer events through electronic health records and to collect samples of colorectal cancer tissue. This funding is from 2017-2021.

In 2017, the NCI contributed funds to ASPREE-XT for all-cause solid tumor tissue to be collected across both countries until January 2019. The collection and banking of cancer tumor tissue will continue and extend to include all cancer subtypes, through the funding of an NIH grant through the National Institute on Aging’s U19 funding mechanism. The continued collection of tumor tissue under the U19 grant will support this biobanking activity during the ASPREE-XT observational study.

At a time in the future and under separate application, the stored tumor tissue will be analyzed to address specific questions regarding the association of biomarkers and major health outcomes. Future applications for ethical approval will be made regarding projects that address disease outcomes of interest observed during the 5 year period of the study. The tumor tissue collection in both countries would improve our ability to measure the longitudinal effects of aspirin on incident and recurrent cancer and metastases, and in turn, potentially lead to the development of preventive and therapeutic targets for these outcomes.

Participant Consent: At the time of the ASPREE-XT consent, each ASPREE participant will be asked to consent to ASPREE-XT investigators obtaining a small sample of tumor tissue collected in the process of cancer diagnosis and/or surgical removal of tumor tissue. Consent will require the ticking of a box at the end of the consent form (see below).

‘Cancer Biopsy
During the course of the study, some people may have biopsies taken for cancer diagnosis. We ask you for permission to access a small sample of this biopsy, if available. ASPREE-XT will not require you to undergo any additional biopsies or procedures for access to this sample. This tumor tissue may be used in future research studies to explore molecular mechanisms of aspirin’s protective effect against cancer, however we cannot yet predict exactly what future research might be performed.

It is possible that the future research on your samples might be performed by other
researchers in Australia or overseas. In that case, some of your samples will be sent to those research laboratories. These samples will be labelled with a code and the scientists at the other laboratories will not be able to identify you from the code. In some cases, the samples we collect are destroyed during the process of testing. Future research on your samples will only be performed with the approval of a Human Research Ethics Committee. We are asking for your ‘unspecified consent’, which means that you agree to allow any type of research to be performed in the future on the samples we obtain for this project.

The purpose of storing your sample is to answer questions in the future, so we expect to keep your tumor sample indefinitely. You can have any sample we obtain removed from our collection and destroyed by contacting the researchers listed in this document in writing.

Please tick the box at the end of this consent form to indicate permission for this access.’

Tumor Tissue Processing, Shipping and Storage:

Australia: ASPREE-XT staff will follow the appropriate procedures for tissue procurement, as dictated by institution from which the tissue is to be sourced (hospital or registry). Procured tumor specimens will be sent to the ASPREE-XT Centre or the Monash Public Health Biorepository, located at the Alfred Hospital, Melbourne, Australia for storage. Application for access to these samples for new analysis projects will be subject to the usual ASPREE (-XT) governance and review, also requiring ethics approval for each project. There is potential for shipment to a US-Based Tissue Procurement Facility (pending project approval and future funding). Upon arrival at the central Monash facility, the tumor tissue will be barcoded, and this code scanned and entered into the Laboratory Information Management System (LIMS) prior to storage. At the time of tumor tissue collection, all relevant information relating to the tissue (e.g. pathology reports, tissue handling and patient case reports) will be copied or scanned, and electronically entered into the ASPREE-XT database. A Tumor Tissue Biospecimen Information Sheet will be completed by the study staff member, identified by only the participant’s ASPREE-XT study number and acrostic, and the information contained therein entered into the ASPREE Healthy Ageing Biobank LIMS. All hard copy Tumor Tissue Biospecimen Information Sheets will be stored in a secure location at the ASPREE Healthy Ageing Biobank.

US: At the time of tumor tissue collection, all relevant information relating to the tissue (e.g. pathology reports, tissue handling and patient case reports) will be copied or scanned, and electronically entered into the ASPREE-XT database. A Tumor Tissue Biospecimen Information Sheet will be completed by the study staff member, identified by only the participant’s ASPREE-XT study number and acrostic, and the information contained therein entered into the ASPREE Healthy Ageing Biobank LIMS. All hard copy Tumor Tissue Biospecimen Information Sheets will be stored in a secure location at the US-Based Tissue Procurement Facility details will be entered into the reporting section dedicated to participant cancer endpoints.

Saliva collection for DNA (Aus only):

Saliva collection can be done in the presence of a study staff member at either a study site, clinic or self-administered within the participant’s home, if deemed more practical. When collected by study staff, a Saliva Biospecimen Information Sheet is completed. When collected by the participant, the participant is asked to complete and return the Saliva Biospecimen Information Sheet with the saliva sample, to the clinic site via pre-paid postage envelope. An instruction sheet will accompany this document, providing clear instructions and further explanations to the questions being asked. Study staff will enter data from the Saliva
Biospecimen Information Sheet to the ASPREE-XT database and mail both the saliva sample and the Saliva Biospecimen Information Sheet within one month or as soon as practical, to the US-Based Tissue Procurement Facility (US specimens). Upon receipt of the Saliva Biospecimen Information Sheet, the study staff will enter final details into the database, and file the original in the participant’s file. The saliva sample will be coded with ASPREE-XT participant ID, entered into the database, and linked to the participants ASPREE-XT study number and acrostic. In Australia, during an ASPREE-XT visit, participants who have not provided a blood or saliva sample to the ASPREE Healthy Ageing Biobank may be approached to provide a saliva sample with consent (PICF) through the ASPREE Healthy Ageing Biobank.