Add-Aspirin Trial

A phase III, double-blind, placebo-controlled, randomised trial assessing the effects of aspirin on disease recurrence and survival after primary therapy in common non-metastatic solid tumours.

Version: 4.0
Date: 13-Nov-2014

MRC CTU ID: AA01
ISRCTN #:
EudraCT #: 2013-004398-28
CTA #:
REC #: 14/SC/0171

Authorised by:

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Date: 13-Nov-2014

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Date: 13-Nov-2014

GENERAL INFORMATION

This document was constructed using the Medical Research Council Clinical Trials Unit at UCL (MRC CTU) Protocol Template Version 4.0. It describes the Add-Aspirin trial, coordinated by the MRC CTU, and provides information about procedures for enrolling participants. This document is the main protocol and provides information relevant to all the tumour site-specific cohorts in the Add-Aspirin study. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to the registered Investigators in the trial, but centres entering participants for the first time are advised to contact the Add-Aspirin trial team (email: mrcctu.add-aspirin@ucl.ac.uk), to confirm they have the most up-to-date version.

PROTOCOL DESIGN

This document is the main protocol for the Add-Aspirin trial. It includes procedures that are common to the four tumour site-specific cohorts and those that are site-specific. The management of each cohort has been aligned where possible to facilitate the analysis of overall survival as the co-primary outcome measure.

COMPLIANCE

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki 2008, the principles of Good Clinical Practice (GCP), Commission Directive 2005/28/EC with the implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the UK Data Protection Act (DPA number: Z5886415), and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF). International centres will comply with the principles of GCP as laid down by the ICH topic E6 (Note for Guidance on GCP) and applicable national regulations.

SPONSOR

University College London (UCL) is the trial sponsor and has delegated responsibility for the overall management of the Add-Aspirin trial to the MRC CTU. Queries relating to UCL sponsorship of this trial should be addressed to the Director of the MRC CTU (Professor Mahesh Parmar), Aviation House, 125 Kingsway, London WC2B 6NH, UK or via the Add-Aspirin Trial Manager.

FUNDING

Cancer Research UK (CRUK), the UK National Institute for Health Research Health Technology Assessment Programme (NIHR HTA) and MRC CTU are funding the Add-Aspirin trial.

Bayer Pharmaceuticals AG are providing the Investigational Medicinal Products (IMPs) – aspirin 300mg with matching placebo, aspirin 100mg with matching placebo and open-label aspirin 100mg for the run-in period.

AUTHORISATIONS AND APPROVALS

Add-Aspirin was approved by the South Central – Oxford C research ethics committee and is part of the UK National Cancer Research Network (NCRN) portfolio.

TRIAL REGISTRATION

Add-Aspirin will be registered with the International Standard Randomised Controlled Trial Number (ISRCTN) Clinical Trials Register.

CLINICAL CENTRES

Add-Aspirin will be open to centres in every Cancer Research Network (CRN) throughout the UK. It is also intended to recruit participants in India. Over time, centres in other countries may also join the trial.

PARTICIPANT REGISTRATION AND RANDOMISATION

REGISTER PARTICIPANTS ONLINE AT:
www.addaspirintrial.org

RANDOMISE PARTICIPANTS BY PHONE:
UK: +44 (0)20 7670 4777 (Mon – Fri, 09:00-17:00 UK time)
India: Details will be confirmed

Email (for all registration or randomisation queries): mrcctu.add-aspirin@ucl.ac.uk

(See section 4)

SERIOUS ADVERSE EVENTS (SAE)

SERIOUS ADVERSE EVENT (SAE) REPORTING IN THE UK
Within 24 hours of becoming aware of an SAE, please send a completed SAE form to the MRC CTU by fax or email (scanned copy):
Fax: +44 (0)20 7670 4818
Email: mrcctu.add-aspirin@ucl.ac.uk

SERIOUS ADVERSE EVENT REPORTING IN INDIA
Details will be confirmed

EMERGENCY UNBLINDING

EMERGENCY UNBLINDING:
www.addaspirintrial.org

See section 5.6 for further details

TRIAL CONTACT DETAILS

FOR FURTHER INFORMATION:
Phone: +44 (0)20 7670 4620 or +44 (0)20 7670 4892
Email: mrcctu.add-aspirin@ucl.ac.uk

TRIAL ADMINISTRATION

Please direct all queries to the Trial Managers at the MRC CTU in the UK or to the Clinical Research Organisation (CRO) in India; clinical queries will be passed to the Chief Investigator (CI), Trial Physician or other members of the Trial Management Group (TMG) as appropriate.

COORDINATING UNIT

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TUMOUR SITE-SPECIFIC LEAD INVESTIGATORS

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Lead Investigator – Breast Cohort (UK)	Dr Alistair Ring	London, UK
Lead Investigator – Colorectal Cohort	Dr Richard Wilson	Belfast, UK
Lead Investigator – Gastro-oesophageal Cohort	Dr Ruth Langley	London, UK
Lead Investigator – Prostate Cohort	Professor Howard Kynaston	Cardiff, UK
Lead Investigator – Translational Research	Professor David Cameron	Edinburgh, UK

INDIA

Lead Investigator – India	Dr Conjeevaram S Pramesh	Mumbai, India
Lead Investigator – Gastro-oesophageal Cohort (India)	Dr Conjeevaram S Pramesh	Mumbai, India
Lead Investigator – Breast Cohort (India)	Professor Sudeep Gupta	Mumbai, India

For full details of all co-investigators please see appendix XII.

SUMMARY OF TRIAL

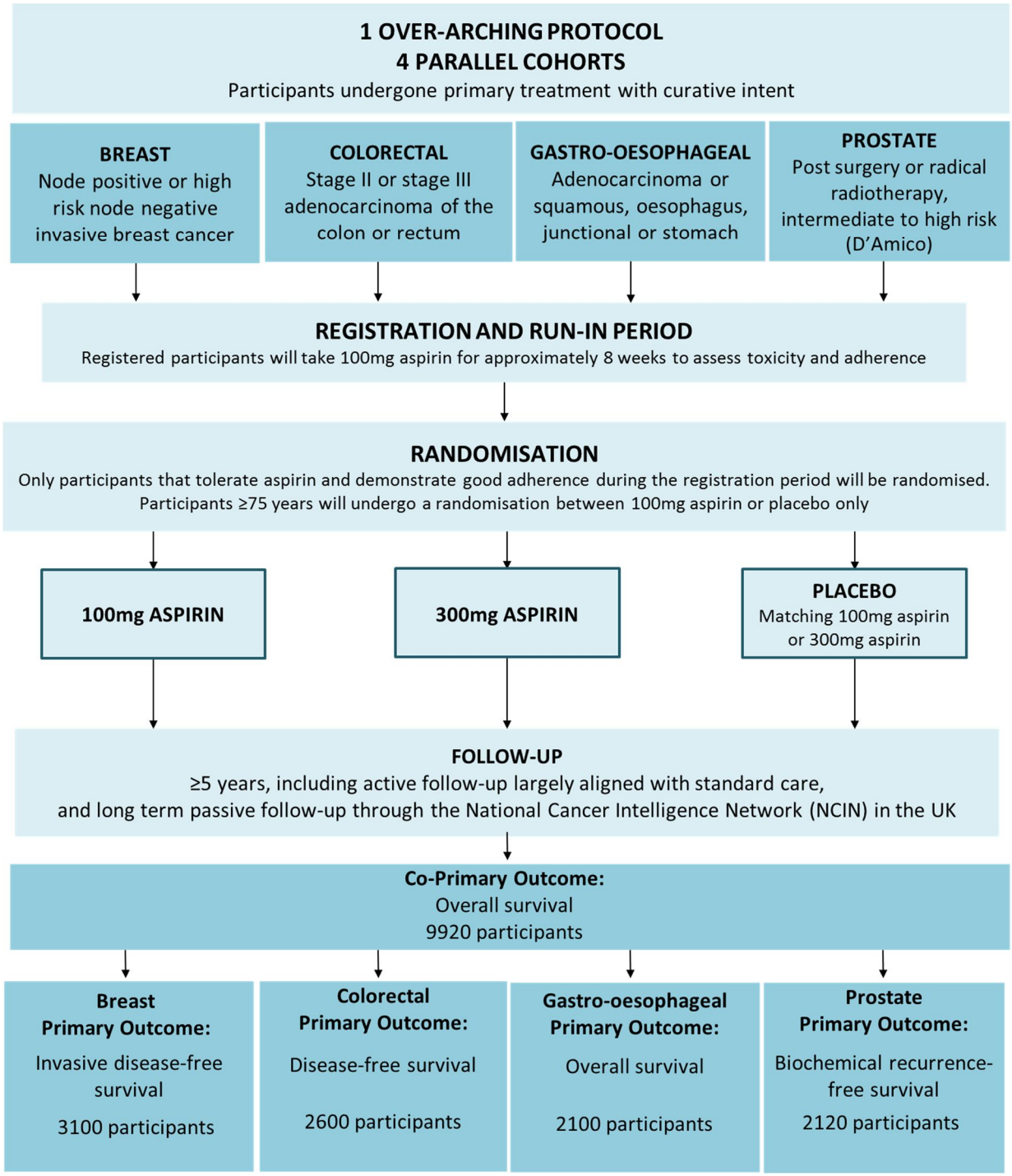
SUMMARY INFORMATION TYPE	SUMMARY DETAILS
Short title of trial	Add-Aspirin
Long title of trial	A phase III, double-blind, placebo-controlled, randomised trial assessing the effects of aspirin on disease recurrence and survival after primary therapy in common non-metastatic solid tumours.
Version	3.0
Date	22-Sep-2014
ISRCTN #	To be confirmed
EudraCT #	2013-004398-28
CTA #	To be confirmed
REC #	14/SC/0171
Study design	A phase III, multi-centre, double-blind, placebo-controlled randomised trial with four parallel cohorts. Each of the four cohorts are tumour site-specific (breast, colorectal, gastro-oesophageal and prostate cancer) see figure 1 – page x. An overarching protocol ensures each cohort is as comparable as possible to allow a combined analysis of overall survival as a co-primary outcome measure as well as allowing individual site-specific analyses. Add-Aspirin incorporates a feasibility phase lasting approximately 2½ years during which recruitment feasibility, treatment adherence and safety will be assessed. During this phase, all participants will take 100mg aspirin daily for a run-in period of approximately 8 weeks prior to randomisation to assess tolerability and adherence.
Study aim	To assess whether regular aspirin use after standard therapy prevents recurrence and prolongs survival in participants with non-metastatic common solid tumours. Standard therapy includes radical surgery or radiotherapy plus any adjuvant or neo-adjuvant therapy, or participation in any pre-approved trials.
Type of participants to be studied	Participants who have undergone potentially curative treatment (surgery or other radical treatment), including any standard neo-adjuvant or adjuvant therapy for breast, colorectal, gastro-oesophageal or prostate cancer or have participated in any pre-approved trials and satisfy the eligibility criteria (see section 3).
Interventions to be compared	Participants will be randomly assigned to 100mg aspirin, 300mg aspirin or matched placebo (see figure 1 – page x). All tablets will be enteric-coated to be taken daily for at least five years. During the feasibility phase of the study, all participants will take open label 100mg aspirin daily for a run-in period of approximately 8 weeks prior to randomisation.

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
Co-primary outcome measures	**All participants:** overall survival **Breast cancer:** invasive disease-free survival **Colorectal cancer:** disease-free survival **Gastro-oesophageal cancer:** overall survival **Prostate cancer:** biochemical recurrence-free survival
Secondary outcome measures	In all participants these will include adherence, toxicity including serious haemorrhage, and cardiovascular events and some tumour site-specific secondary outcome measures.
Registration and randomisation	Participants can be registered online for the run-in period through the trial website (www.addaspirintrial.org). Following assessment at the end of the run-in period, eligible participants can be randomised by phone (+44 (0)20 7670 4777). See section 4 for further details of this process. Participants will undergo a double-blind randomisation and will be allocated in a 1:1:1 ratio to either 100mg aspirin, 300mg aspirin or a matched placebo. The randomisation will use minimisation with a random element, balancing for key prognostic factors. Participants who are 75 years old or over, will only be allocated to either 100mg aspirin or matched placebo.
Number of participants to be randomised (UK and India)	Total: 9920 participants Breast: 3100 participants Colorectal: 2600 participants Gastro-oesophageal: 2100 participants Prostate: 2120 participants
Duration	Participants will be recruited over 3 to 6 years depending on tumour site and will self-administer tablets daily for at least 5 years. UK participants will be actively followed for at least 5 years after randomisation. Long-term passive follow-up data will be obtained from routinely-collected healthcare databases for at least 10 further years. Indian participants will be actively followed-up for at least 10 years after randomisation. Tumour site-specific primary analyses will take place 5-6 years after recruitment of the last participant for that cohort, and a later, long-term analysis is also planned. The co-primary outcome measure, overall survival in all participants will be assessed after 15 years.

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
Ancillary studies/sub studies	▪ Adherence in a sub-set of UK participants will be assessed by measuring serum thromboxane B_2, a product of platelet aggregation, which will provide an indicator of cyclooxygenase activity. ▪ Blood and tissue samples will be prospectively collected for future translational projects. A number of studies are expected to be initiated whilst the trial is ongoing (subject to funding). ▪ A methodological sub-study will compare the quality and completeness of routinely-collected healthcare data with data collected within the trial, with the aim of assessing the suitability of passive follow-up data collection for investigating long-term primary and secondary outcome measures within the trial. ▪ There will also be methodological sub-studies into trial conduct including site recruitment and initiation.
Sponsor	University College London for the UK
Funders	▪ Cancer Research UK ▪ National Institute Health Research (NIHR) Health Technology Assessment Programme (HTA) ▪ Bayer Pharmaceuticals AG has agreed to provide the Investigational Medicinal Products (IMPs) ▪ MRC Clinical Trials Unit at UCL
Co-ordinator in India	▪ Tata Memorial Hospital

TRIAL SCHEMA

Figure 1. Trial Entry, Randomisation and Treatment



TRIAL ASSESSMENT SCHEDULE

BREAST COHORT

	MONTHS SINCE RANDOMISATION (EXCEPT WHERE INDICATED)													
	PRIOR TO REGISTRATION	PRIOR TO RANDOMISATION (END OF RUN-IN PERIOD)	3	6	9	12	18	24	30	36	42	48	54	60
Blood tests: FBC, LFT, U&E & eGFR	✓	✓		✓		✓		✓		✓		✓		✓
Fasting lipid profile	✓													
C-Reactive Protein (CRP)	✓			✓		✓								
Symptoms & toxicity assessment[1]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Cognitive assessment[1] (Montreal Cognitive Assessment)	✓					✓								✓
Treatment adherence[1]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Concomitant medication[1]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Clinical assessment	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Blood pressure check[2]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Weight[2]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Height	✓													
Comorbidity assessment	✓													
VES-13 questionnaire[3]	✓													✓
Mammography	✓					✓		✓		✓		✓		✓
Tumour and blood sample to be stored in bio-bank[4]	✓													
Blood sample for thromboxane B_2 study[4] (selected centres only)		✓												

1. It is preferable if all follow-up visits are in person and all tests are done at the time of consultation, however this may not be in-line with practices at all centres and can be done over the telephone where no visit is possible.
2. Please take blood pressure and weight only during routine clinic visits. Where not due to attend clinic, this is not mandatory.
3. 65 years and over at registration.
4. Where participants have given their consent.

N.B. Imaging examinations will be aligned to standard practice +/- 6 months. Additional imaging examinations should be performed if clinically indicated.

COLORECTAL COHORT

	MONTHS SINCE RANDOMISATION (EXCEPT WHERE INDICATED)													
	PRIOR TO REGISTRATION	PRIOR TO RANDOMISATION (END OF RUN-IN PERIOD)	3	6	9	12	18	24	30	36	42	48	54	60
Blood tests: FBC, LFT, U&E & eGFR	✓	✓		✓		✓		✓		✓		✓		✓
Fasting lipid profile	✓													
C-Reactive Protein (CRP)	✓			✓		✓								
Symptoms & toxicity assessment[1]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Cognitive assessment[1] (Montreal Cognitive Assessment)	✓					✓								✓
Treatment adherence[1]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Concomitant medication[1]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Clinical assessment	✓		✓	✓		✓	✓	✓		✓				✓
Blood pressure check[2]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Weight[2]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Height	✓													
Comorbidity assessment	✓													
VES-13 questionnaire[3]	✓													✓
CEA test	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
CT (chest, abdomen, pelvis)						✓		✓						✓
Colonoscopy							✓		✓					✓
Tumour and blood sample to be stored in bio-bank[4]	✓													
Blood sample for thromboxane B_2 study[4] (selected centres only)		✓												

1. It is preferable if all follow-up visits are in person and all tests are done at the time of consultation, however this may not be in-line with practices at all centres and can be done over the telephone where no visit is possible.
2. Please take blood pressure and weight only during routine clinic visits. Where not due to attend clinic, this is not mandatory.
3. 65 years and over at registration.
4. Where participants have given their consent.

N.B. Imaging examinations will be aligned to standard practice +/- 6 months. Additional imaging examinations should be performed if clinically indicated.

GASTRO-OESOPHAGEAL COHORT

	MONTHS SINCE RANDOMISATION (EXCEPT WHERE INDICATED)													
	PRIOR TO REGISTRATION	PRIOR TO RANDOMISATION (END OF RUN-IN PERIOD)	3	6	9	12	18	24	30	36	42	48	54	60
Blood tests: FBC, LFT, U&E & eGFR	✓	✓		✓		✓		✓		✓		✓		✓
Fasting lipid profile	✓													
C-Reactive Protein (CRP)	✓			✓		✓								
Symptoms & toxicity assessment[1]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Cognitive assessment[1] Montreal Cognitive Assessment)	✓					✓								✓
Treatment adherence[1]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Concomitant medication[1]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Clinical assessment	✓		✓	✓		✓	✓	✓		✓				✓
Blood pressure check[2]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Weight[2]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Height	✓													
Comorbidity assessment	✓													
VES-13 questionnaire[3]	✓													✓
Tumour and blood sample to be stored in bio-bank[4]	✓													
Blood sample for thromboxane B_2 study[4] (selected centres only)		✓												

1. It is preferable if all follow-up visits are in person and all tests are done at the time of consultation, however this may not be in-line with practices at all centres and can be done over the telephone where no visit is possible.
2. Please take blood pressure and weight only during routine clinic visits. Where not due to attend clinic, this is not mandatory.
3. 65 years and over at registration.
4. Where participants have given their consent.

N.B. Imaging examinations for all studies can be performed approximately +/- 6 months from the time-point indicated above. Additional imaging examinations should be performed if clinically indicated.

PROSTATE COHORT

	MONTHS SINCE RANDOMISATION (EXCEPT WHERE INDICATED)													
	PRIOR TO REGISTRATION	PRIOR TO RANDOMISATION (END OF RUN-IN PERIOD)	3	6	9	12	18	24	30	36	42	48	54	60
Blood tests: FBC, LFT, U&E & eGFR	✓	✓		✓		✓		✓		✓		✓		✓
Fasting lipid profile	✓													
C-Reactive Protein (CRP)	✓			✓		✓								
Symptoms & toxicity assessment[1]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Cognitive assessment[1] Montreal Cognitive Assessment)	✓					✓								✓
Treatment adherence[1]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Concomitant medication[1]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Clinical assessment	✓		✓	✓		✓	✓	✓		✓				✓
Blood pressure check[2]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Weight[2]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Height	✓													
Comorbidity assessment	✓													
VES-13 questionnaire[3]	✓													✓
PSA test	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Tumour and blood sample to be stored in bio-bank[4]	✓													
Blood sample for thromboxane B_2 study[4] (selected centres only)		✓												

1. It is preferable if all follow-up visits are in person and all tests are done at the time of consultation, however this may not be in-line with practices at all centres and can be done over the telephone where no visit is possible.
2. Please take blood pressure and weight only during routine clinic visits. Where not due to attend clinic, this is not mandatory.
3. 65 years and over at registration.
4. Where participants have given their consent.

N.B. PSA tests will be aligned to standard practice +/- 6 weeks for three-monthly testing and +/- 6 months for annual testing. Additional tests should be performed if clinically indicated.

CONTENTS

ABBREVIATIONS

Abbreviation	Expansion
AE	Adverse event
AMD	Age-related macular degeneration
AR	Adverse reaction
ATTC	Antithrombotic Trialists Collaboration
BC	Breast cancer
BNF	British National Formulary
bRFS	Biochemical recurrence-free survival
CEA	Carcinoembryonic antigen
CI	Chief Investigator
CI	Confidence interval
Cox	Cyclooxygenase
CRC	Colorectal cancer
CRF	Case report form
CRN	Cancer Research Network
CRO	Clinical Research Organisation
CRP	C-reactive protein
CRUK	Cancer Research UK
CTA	Clinical trials authorisation
CTCAE	Common terminology criteria for adverse events
CTU	Clinical Trials Unit
DCIS	Ductal carcinoma in situ
DFS	Disease free survival
DNA	Deoxyribonucleic acid
DPA	(UK) Data Protection Act

Abbreviation	Expansion
EC	European Commission
eGFR	Estimated glomerular filtration rate
ER	Estrogen receptor
EU	European Union
EudraCT	European Union Drug Regulatory Agency Clinical Trial
FBC	Full blood count
G6PD	Glucose-6-phosphate dehydrogenase
GCP	Good clinical practice
GI	Gastrointestinal
GP	General Practitioner
HER2	Human epidermal growth factor
HPFS	Health Professional Follow-up Study
HR	Hazard ratio
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IMP	Investigational medicinal product
IRB	Institutional Review Board
ISRCTN	International Standard Randomised Controlled Trial Number
IDFS	Invasive disease-free survival
LFT	Liver function tests
LHRH	Lutenising hormone releasing hormone
MDT	Multi-disciplinary team
MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical Research Council
MRC CTU	Medical Research Council Clinical Trials Unit at UCL

Abbreviation	Expansion
NCIN	National Cancer Intelligence Network
NCRI	National Cancer Research Institute
NCRN	National Cancer Research Network
NHS	National Health Service
NICE	UK National Institute for Health and Clinical Excellence
NIHR HTA	National Institute for Health Research Health Technology Assessment Programme
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratio
OS	Overall survival
PC	Prostate cancer
PCSS	Prostate cancer-specific survival
PI	Principal Investigator
PIS	Participant information sheet
PPI	Proton pump inhibitor
PTGS	Prostaglandin endoperoxide synthetase
PSA	Prostate specific antigen
QA	Quality assurance
QC	Quality control
R&D	Research and development
REC	Research Ethics Committee
RGC	Research Governance Committee
RGF	Research Governance Framework (for Health and Social Care)
RR	Relative risk
SAE	Serious adverse event
SAR	Serious adverse reaction
SPC	Summary of Product Characteristics

Abbreviation	Expansion
SSA	Site-specific approval
SSI	Site-specific information
SUSAR	Suspected unexpected serious adverse reaction
TM	Trial Manager
TMF	Trial master file
TMG	Trial Management Group
TMH	Tata Memorial Hospital
TSC	Trial Steering Committee
UAR	Unexpected adverse reaction
UCL	University College London
U&E	Urea & electrolytes
UK	United Kingdom
ULN	Upper limit of normal
US	United States
WHO	World Health Organisation

1 BACKGROUND

1.1 INTRODUCTION

Cancer is a global problem and the third most common cause of death worldwide,[1] with an estimated 14.1 million cases and 8.1 million deaths in 2012.[2] Add-Aspirin includes participants with breast, colorectal, gastro-oesophageal and prostate tumours which, together, accounted for approximately one third of all cancer cases and cancer deaths in 2012. In the UK, breast, colorectal and prostate cancer are the three most common cancers after lung cancer and, whilst the incidence of gastro-oesophageal cancer is lower, due to poorer outcomes it still ranks amongst the highest in terms of cancer deaths.[2]

Although cancer is often thought to be a disease of higher income populations, almost two-thirds of cancer deaths occur in lower income countries. Gastro-oesophageal tumours are more common in economically developing countries.[3] The prevalence of breast, colorectal and prostate cancer is lower, but cases are increasing. Furthermore, outcomes are poorer than in higher income countries, in part due to lack of access to treatments. By 2030, cancer deaths are expected to rise to 11.8 million per year globally, largely due to longer life expectancy, particularly in low and middle income countries where declines in communicable diseases are leading to an ageing population.[1, 4] There is growing concern about the global economic burden of cancer and other chronic diseases. [5, 6] Increasing costs of cancer care are attributed to both increasing incidence and the rising costs of treatments, and measures proposed to stem this include innovation in low-cost technologies such as generic drugs.[7]

Participants entering Add-Aspirin will have undergone potentially curative treatment (radical surgery or (chemo)radiotherapy as appropriate) and any standard adjuvant therapy for breast, colorectal, gastro-oesophageal or prostate cancer. Avoiding recurrent disease, subsequent treatment and mortality in these participants is an important goal. The selected disease sites are those for which (i) the evidence relating to a potential benefit of aspirin is strongest; (ii) the potential impact is large (common cancers with large numbers of cases diagnosed at an early stage, or where outcomes of curative treatment are particularly poor); and (iii) recruitment is feasible. In order to have an impact globally on cancer outcomes, there is a need to identify adjuvant treatments that are effective, relatively low-cost, and feasible to administer in both resource poor and rich countries. Research into cancer treatments increasingly focuses on developing new, and usually expensive, agents and regimens, placing a growing strain on health services globally. As a low-cost pharmaceutical with the potential to improve cancer outcomes, in addition to other possible health benefits (such as cardiovascular effects), aspirin warrants further investigation as an anti-cancer agent in well-designed international studies.

1.2 RATIONALE FOR AN ANTI-CANCER EFFECT OF ASPIRIN

There is a considerable body of preclinical data, epidemiological studies, and meta-analyses of randomised data to support the hypothesis that aspirin has the potential to be an effective adjuvant cancer therapy. This has been described in a previous systematic review,[8] and is summarised in the next two sections including recent significant developments.

1.2.1 POTENTIAL MECHANISMS OF ACTION FOR AN ANTI-CANCER EFFECT OF ASPIRIN

Aspirin inhibits both isoforms of the enzyme cyclooxygenase (Cox), also known as prostaglandin endoperoxide synthetase (PTGS) but preferentially inhibits Cox-1. Cox converts arachadonic acid to

prostaglandin H2 which produces biologically active prostaglandins that influence pathophysiological processes in a range of tissues including the inflammatory response, thrombosis, and cell proliferation and migration.[9] Clinically, to date, aspirin has mainly been used as an analgesic/anti-inflammatory and in the treatment and prevention of cardiovascular disease since it prevents platelet aggregation. The first indication of a possible role for aspirin in cancer therapy was reported over four decades ago, with both platelet reduction and aspirin administration associated with a significant reduction in metastases in mice.[10]

Many of the downstream mediators of the Cox pathways are thought to be involved in the development and spread of malignancy.[11] Aspirin, however, has a short half-life (approximately 20 minutes) and, although it irreversibly inactivates Cox-1 and Cox-2 through selective acetylation, nucleated cells can resynthesise Cox isozymes within a few hours. Thus, a single daily dose of aspirin (75–100mg), as used in the contemporary vascular studies analysed by Rothwell[12-14] and the recent observational cohort studies[15, 16] (described below and showing positive effects on cancer outcomes), is unlikely to have been caused by a direct effect on Cox pathways in systemic tissues. A divided daily dose of >2000mg of aspirin would be required to achieve consistent inhibition of Cox in tissues.[17]

A once daily dose of aspirin (75–100mg) is considered to have negligible direct biological effects apart from on the anucleate platelet through inhibition of Cox-1. Platelets are thought to affect the development and spread of metastases by facilitating the adhesion of cancer cells to circulating leukocytes and endothelial cells, and permitting adhesion to the endothelium and transmigration.[18] They may also protect circulating cancer cells from immune-mediated clearance by natural killer cells.[19] It is also thought that platelets may play a more active role in promoting metastatic spread outside of the primary tumour's microenvironment by active signalling to tumour cells through the TGF-β and NF-kappa B pathways resulting in a pro-metastatic phenotype that facilitates tumour cell extravasation and metastasis formation.[20]

There is also a significant body of evidence indicating that selective Cox-2 inhibitors are potentially useful anti-cancer agents, and they have been shown to prevent adenoma formation in randomised trials.[21] It has been suggested that inhibition of Cox-1 in platelets by low-dose aspirin suppresses the induction of Cox-2 in distant nucleated cells within the tumour or stromal environment in the early stages of neoplasia.[17] At sites of intestinal mucosal injury, platelets trigger downstream signalling events leading to reduced apoptosis, enhanced cellular proliferation and angiogenesis, which can be indirectly inhibited by aspirin. This would explain the observations that both daily low-dose aspirin and selective Cox-2 inhibitors appear to be effective anti-cancer drugs and is supported by studies showing that inhibition of either Cox-1 or Cox-2 is sufficient to inhibit tumourigenesis in mouse models.[22] Whilst the maximum anti-platelet effect of daily aspirin is thought to occur with <100mg aspirin, it has been proposed that higher doses may have additional biological effects and therefore in this study, a higher dose will also be evaluated.

In the Nurses' Health Study and Health Professional Follow-Up Study (HPFS) – detailed further below – improvements in cancer outcomes with regular aspirin use after a diagnosis of colorectal cancer, were largely restricted to tumours that overexpressed Cox-2,[23] and if the tumours had mutated *PIK3CA,*[24] raising the possibility that molecular profiling may be able to select patients most likely to respond to aspirin. In the Nurses' Health Study, although similar benefits were seen with aspirin use after a breast cancer diagnosis the relationship with Cox-2 expression was not confirmed.[25] Although the numbers of colorectal cancer patients with mutated *PIK3CA* who regularly used aspirin in this study was small (n=66), the results were marked, with a multivariate hazard ratio (HR) for cancer death of 0.18 (95% confidence interval (CI) 0.06-0.61, p<0.001), and 0.54 (95% CI 0.31-0.94, p=0.01), for death from any cause for those that regularly took aspirin after a

diagnosis of colorectal cancer. This is also supported by a sub-analysis of the VICTOR trial (a randomised placebo controlled trial of rofecoxib after primary colorectal cancer resection which was closed early after the worldwide withdrawal of rofecoxib). Those with mutated PIK3CA who reported regular aspirin use had lower recurrence rates (HR= 0.11; 95% CI, 0.001 to 0.832; P=0.027) compared to those lacking PIK3CA mutations (HR= 0.92, 95% CI, 0.60 to 1.42; P= 0.71),[26] although again the numbers are small (14 of 104 patients with mutated PIK3CA reported regularly using aspirin). Given the relatively low frequency of *PIK3CA* mutations (15-20%) in colorectal cancer, it is unlikely that an effect on the mutated *PIK3CA* tumours alone could explain the large effects of aspirin on colorectal cancer incidence and mortality observed in the randomised vascular trials. Results from other studies aiming to confirm this association have produced conflicting results[27, 28] and, to date, the available data are from non-randomised studies or sub-group analyses with small sample sizes where confounding factors may be an issue. Thus further robust data from other studies will be required to test this potential association.

As well as inhibiting Cox, aspirin has additional mechanisms of action that may contribute to anti-tumour effects through Cox-independent pathways.[29] It inhibits activation of NF-kappa B,[30] which is thought to play a key role in tumour growth and invasion,[31] as well as promoting apoptosis,[32] inhibiting angiogenesis[33] and interacting with other cell cycle regulators and signalling pathways that are thought to influence the development and growth of malignancies.[34] *In vitro* evidence also demonstrates that aspirin can potentially interact directly with other molecules and pathways implicated in tumourigenesis, including B-catenin and wnt signalling, tumour necrosis factor, polyamine metabolism and the deoxyribonucleic acid **(**DNA) mismatch repair system.[34-36]

1.2.2 CLINICAL EVIDENCE: META-ANALYSES OF CARDIOVASCULAR TRIALS

In a series of individual patient data meta-analyses of randomised controlled trials primarily designed to assess the cardiovascular benefits of aspirin, Rothwell and colleagues have shown marked reductions in cancer incidence and cancer mortality associated with regular aspirin use (> 3 years) in both the short- and long-term[12-14, 37, 38]. An analysis of seven trials (>23,000 patients) showed a reduction in deaths from all cancers after 5 years of follow up (HR=0.66, 95% CI 0.5-0.87, p=0.003) and an absolute reduction in 20-year risk of cancer death of 7% for those over 65 years.[13] The effect was largest for adenocarcinomas (HR=0.53, 95% CI 0.35-0.81) and for gastro-intestinal cancers (HR=0.46, 95% CI 0.27-0.77). Analyses of the effects on individual cancers are likely to be underpowered, but significant effects were seen for colorectal and pancreatic cancer, with strong (though not statistically significant) trends for oesophageal, prostate and lung (breast cancer was not analysed separately due to insufficient data).

Since short-term effects on cancer mortality were seen, as well as longer-term effects on incidence, the meta-analysis data suggested that aspirin has a potential role in the treatment as well as prevention of cancer. This hypothesis has been supported by a subsequent analysis of a subset of the trials which indicated that aspirin decreases the risk of metastases (HR=0.64, 95% CI 0.48-0.84) and this is likely to contribute to the overall reduction in fatal cancers.[38] In individuals diagnosed with incident adenocarcinoma during the trials, survival was better in those allocated to aspirin (HR=0.71, 95% CI 0.57-0.90) and, although analyses for individual cancers were, again, underpowered, strong trends were observed for risk of colorectal, breast and prostate cancer deaths (HRs 0.27, 95% CI 0.11-0.66, p=0.004; 0.16, 95% CI 0.02-1.19 p=0.07; and 0.34, 95% CI 0.12-0.99, p=0.05 respectively).

1.2.3 CLINICAL EVIDENCE: EPIDEMIOLOGICAL AND RANDOMISED DATA

The first epidemiological study to show that regular aspirin use was associated with a decreased risk of developing cancer was published in 1988.[39] Since then there have been well over 100 case-control

and cohort studies investigating the use of aspirin and cancer risk.[40] In a recently updated review of such studies, significant reductions in risk of cancer associated with aspirin use were observed for a number of individual disease sites, most notably cancers of the digestive tract (colorectal, gastric, adenocarcinoma of the oesophagus/cardia and squamous cell carcinoma of the oesophagus), but also for breast and prostate cancers (see table 1).

Table 1: Summary of relative risks* - Bosetti *et al*.[40]

CANCER TYPE/STUDY	NO. OF STUDIES	NO. OF CASES	RELATIVE RISK (RR) (95% CI)
Colorectal cancer			
Case-control	15	21,414	0.63 (0.56-0.70)
Cohort	15	16,105	0.82 (0.75-0.89)
Overall	**30**	**37,519**	**0.73 (0.67-0.79)**
Gastric cancer			
Case-control	7	2411	0.60 (0.44-0.82)
Cohort	6	2108	0.77 (0.58-1.04)
Overall	**13**	**4519**	**0.67 (0.54-0.83)**
Oesophageal/cardia adenocarcinoma			
Case control	9	3222	0.60 (0.48-0.75)
Cohort	2	499	0.88 (0.68-1.15)
Overall	**11**	**3721**	**0.64 (0.52-0.78)**
Oesophageal Squamous Cell Carcinoma/unknown			
Case-control	7	1075	0.54 (0.44-0.67)
Cohort	4	1118	0.73 (0.51-1.07)
Overall	**11**	**2193**	**0.61 (0.50-0.76)**
Breast			
Case-control	10	28,835	0.83 (0.76-0.91)
Cohort	22	27,091	0.93 (0.87-1.00)
Overall	**32**	**52,926**	**0.90 (0.85-0.95)**
Prostate			
Case-control	9	5795	0.87 (0.74-1.02)
Cohort	15	31,657	0.91 (0.85-0.97)
Overall	**24**	**37,452**	**0.90 (0.85-0.96)**

*Summary of relative risks of developing cancer in regular aspirin users (at least 1-2 tablets per week) compared to non-users in several common solid tumours

Further details of the evidence pertaining to individual cancer sites is given in the next section.

Although two large placebo-controlled randomised trials (the Physicians' Health Study and the Women's Health Study) of alternate day aspirin (100mg or 325mg) as a primary prevention strategy did not initially show an improvement in cancer outcomes,[41, 42] extended follow-up in the Women's Health Study found that a reduction in colorectal cancer incidence emerged after 10 years in the aspirin group (HR, 0.80, CI 0.67 to 0.97, p=0.021)[43]. Furthermore, Burn *et al*. have recently published the first positive results from a randomised trial designed to demonstrate that aspirin can prevent the development of cancer.[44] The CAPP2 trial demonstrated that 600mg of aspirin daily for up to 4 years prevents colorectal and other cancers associated with Lynch syndrome (a hereditary condition which predisposes to the development of cancer due to mutations in DNA repair genes). The HR for risk of all Lynch syndrome related cancers was 0.45 (95% CI 0.26-0.79, p=0.0005) in favour of aspirin in those patients who remained on treatment for at least 2 years.

1.3 RATIONALE FOR A THERAPEUTIC ROLE OF ASPIRIN IN SPECIFIC TUMOUR TYPES

In addition to the above evidence suggesting overall anti-cancer effects of aspirin, some of the key results pertaining to each of the included tumour sites is discussed below. Other tumour sites may be considered for inclusion in the trial, particularly if new external data emerge.

1.3.1 BREAST CANCER

In addition to the evidence discussed in section 1.2 suggesting overall anti-cancer effects of aspirin, some of the key results pertaining to breast cancer are highlighted here. The epidemiological data supporting the inclusion of breast cancer patients in this study is particularly strong. In the review by Bosetti *et al.* the relative risk of developing breast cancer in aspirin users was 0.83 (95% CI 0.76-0.91) in 10 case-control studies, and 0.93 (95% CI 0.87-1.00) in 22 cohort studies.[40] More pertinent to the Add-Aspirin trial, results from the Nurses' Health Study indicated that aspirin use following a diagnosis of breast cancer may reduce the risks of breast cancer death, breast cancer recurrence and death from any cause[45] (see table 2 – page 29). In 4,164 female US nurses diagnosed with stage I-III breast cancer in the study, aspirin use was associated with a decreased risk of breast cancer death with adjusted relative risks for 1, 2 to 5 and 6 to 7 days of aspirin use per week of 1.07 (95% CI 0.70-1.63), 0.29 (95% CI 0.16-0.52), and 0.36 (95% CI 0.24-0.54) respectively compared with no use (test for linear trend, p<0.001). This association did not differ appreciably by stage, menopausal status, body mass index, or oestrogen receptor status. Algra and Rothwell have recently shown that the associations between aspirin use and death from cancer seen in observational studies correlate well with those observed in randomised controlled trials.[46]

1.3.2 COLORECTAL CANCER

The most extensive evidence relating to the anti-cancer effects of aspirin pertains to colorectal cancer. Some of the key studies have been discussed in the preceding section with the colorectal cancer-specific results highlighted here. The first epidemiological evidence that aspirin could act as a chemoprevention agent was the report by Kune *et al.* in 1988 of a case-control study, in which aspirin use was associated with a significantly lower risk of colorectal cancer even after adjustment for other risk factors.[39] In the aforementioned systematic review by Bosetti and colleagues, analysis of 30 case-control and cohort studies indicated that aspirin use was associated with a lower risk of developing colorectal cancer (relative risk (RR)=0.73, 95% CI 0.67-0.79).[40] A role for aspirin in the secondary prevention of colorectal adenomas has been demonstrated. In a meta-analysis of four randomised trials of patients previously diagnosed with colorectal cancer or adenomas, aspirin reduced the risk of further adenomas by 18% (RR=0.82, 95% CI 0.74-0.91), with similar estimates for doses <300mg (RR=0.82, 95% CI 0.70-0.95, p=0.007) or >300mg (RR=0.84, 95% CI 0.74-0.94, p=0.004) of aspirin daily.[47] The cancer outcome data from the randomised cardiovascular trials assessing aspirin has consistently shown significant reductions in cancer deaths from adenocarcinomas arising from the gastrointestinal tract, and particularly colorectal cancers (HR=0.61, 95% CI 0.43-0.87).[12, 13, 37, 38] Data from the CAPP2 trial and the Women's Health Study, as described earlier, also support the inclusion of colorectal cancer patients in Add-Aspirin.[43, 44]

Additional evidence of a potential role for aspirin as an adjuvant treatment for colorectal cancer comes from non-randomised studies (see table 2 – page 29). In the Nurses' Health Study and HPFS, two large, prospective studies, aspirin use after a diagnosis of colorectal cancer was associated with a significant reduction in colorectal cancer deaths (adjusted HR=0.71, 95% CI 0.53-0.95), as well as overall mortality, with larger effects observed for daily users.[23] A large Dutch population-based study has shown a reduction in overall mortality associated with aspirin use following a colon cancer diagnosis (adjusted RR 0.65, 95% CI 0.50-0.84),[48] and similar results have been observed in an audit of colorectal cancer patients in Tayside and Fife (adjusted HR=0.67, 95% CI 0.57-0.79).[15] Many of the

in vitro studies investigating potential mechanisms by which aspirin has anti-cancer effects have been performed in colorectal cell lines.[49-51]

1.3.3 GASTRO-OESOPHAGEAL CANCER

In addition to the evidence discussed in section 1.2 suggesting overall anti-cancer effects of aspirin, some of the key results pertaining to gastro-oesophageal cancer are highlighted here. The rationale for including gastro-oesophageal tumours in this study is also strong and is supported by *in vitro* data.[52, 53] In the review by Bosetti *et al.*, aspirin was associated with relative risks of 0.61 (95% CI 0.50-0.76) for developing squamous cell oesophageal cancer, 0.64 (0.52-0.78) for adenocarcinoma of the oesophagus or gastric cardia and 0.67 (95% CI 0.54-0.83) for stomach cancer.[40] As described above, the data from Rothwell and colleagues from cardiovascular randomised controlled trials show consistent positive effects on the incidence and mortality from gastrointestinal cancer (HR=0.46, 95% CI 0.27-0.77)[13] with similar effects seen in both observational studies and the trial data for both gastric and oesophageal tumours.[46] There are also preliminary data from a controlled trial (not fully randomised) in China evaluating aspirin after resection for squamous cell carcinoma of the oesophagus or adenocarcinoma of the cardia (n=1600)[54] (see table 2 – page 29). Five-year survival was 51%, 41% and 42% for patients on aspirin, placebo and no tablet respectively (p=0.04 for the difference between treatments), with effects seen for both squamous cell and adenocarcinoma patients.

1.3.4 PROSTATE CANCER

In addition to the evidence discussed in section 1.2 suggesting overall anti-cancer effects of aspirin, some of the key results pertaining to prostate cancer are highlighted here. The clearest evidence to support the Add-Aspirin prostate cohort hypothesis comes from published data from the multi-centre CaPSURE (Cancer of the Prostate Strategic Urologic Research) database[55] (see table 2 – page 29). In nearly 6,000 men who had undergone radical treatment (surgery or radiotherapy) for prostate cancer, with median follow-up 70 months, anti-coagulant use was associated with a reduction in prostate cancer-specific mortality, as well as reductions in bone metastases and disease recurrence. The effects were largely attributed to aspirin, which was the anti-coagulation therapy used by the majority of men (83%), with a HR for prostate cancer-specific mortality of 0.43 (95% CI 0.21-0.87) for aspirin users. The largest effects were observed for men with a high risk of disease recurrence, with estimated 10-year prostate cancer-specific mortality of 4% for anti-coagulant users vs 19% for non-users, p<0.01. In a large retrospective series, aspirin non-use was associated with early biochemical failure after prostate irradiation therapy (OR 2.052 p=0.0012 95% CI 1.328-3.172).[56]

Further evidence for an effect of aspirin in prostate cancer comes from the most recent review of observational studies suggesting that the relative risk of developing prostate cancer is reduced by 10% in regular aspirin users, with similar risk reductions reported in both case-control and cohort studies, and for both low-grade and high-grade, more aggressive tumours.[57] As in the other tumour sites, there are *in vitro* studies investigating the effects of aspirin in tumour cell lines [58, 59] and supporting data from the meta-analyses by Rothwell *et al.* where, though the analyses for individual cancers were underpowered, there was a strong trend towards a reduction in prostate cancer deaths associated with aspirin after 5 years of follow-up (HR=0.52, 95% CI 0.20-1.34). Given the concerns about cardiovascular toxicity with long-term androgen deprivation in the treatment of prostate cancer, there may be additional benefits from incorporating aspirin into treatment algorithms for prostate cancer.[60] Recent results from the STAMPEDE trial indicated that celecoxib (a Cox-2 inhibitor) showed insufficient activity as an addition to lutenising hormone releasing hormone analogue (LHRHa) treatment for locally advanced and metastatic prostate cancer to warrant continued evaluation.[61] This does not, however, undermine the rationale for the Add-Aspirin

prostate cohort since, as discussed above, the hypothesized mechanism by which aspirin in the dose range 75-300mg daily has anti-cancer effects is not direct inhibition of Cox-2 in systemic tissues for which a divided dose of 2000mg daily would be required.[17]

Table 2: Summary of observational data assessing the effects of aspirin after a cancer diagnosis by tumour type

TUMOUR	STUDY AND SAMPLE SIZE	RISK REDUCTION WITH ASPIRIN (EXCEPT WHERE INDICATED)
Colorectal cancer (CRC)	Nurses' Health and HPFS, Chan *et al*. 2009[23] n=1279	CRC mortality HR 0.71 (0.53-0.95) All-cause mortality HR 0.79 (0.65-0.97)
	Bastiaannet *et al*. 2012[16] n=4481	Overall survival (OS) RR 0.65 (0.50-0.84)
	McCowan et al. 2012[15] n=2990	CRC mortality HR 0.67 (0.57-0.79) Overall mortality HR 0.58 (0.45-0.75)
Breast cancer (BC)	Nurses' Health Study, Holmes *et al*. 2010[45] n=4164	BC mortality RR 0.36 (0.24-0.65) with daily use Overall mortality RR 0.54 (0.41-0.70) with daily use
Prostate cancer (PC)	Zaorsky *et al*. 2012[56] n=2051 (post-radiotherapy)	Interval to biochemical failure in aspirin non-users vs users odds ratio (OR) 2.05 (1.33-3.17)
	CaPSURE study, Choe *et al*. 2012[62] n=5995 (post-radical therapy)	PC mortality HR 0.43 (0.21-0.87)
Gastro-oesophageal cancer	Liu *et al*. 2009[54] n=1600	5-year OS aspirin 51.2%, placebo 41%, no tablet 42.3%. No HR/RR presented.

1.4 ASPIRIN TOXICITY AND RISK-BENEFIT CONSIDERATIONS

The use of aspirin as a primary prevention strategy against cancer has been limited by concerns about toxicity, particularly serious haemorrhage.[63] Previous reports of rates of serious bleeding from clinical trials of anti-platelet agents are often inconsistent. This is likely to be due to the lack of a standardised definition of serious bleeding.[64] In a meta-analysis of six randomised controlled trials of primary cardiovascular prevention (n>95,000, mean age 56 years, 46% male) by the Antithrombotic Trialists Collaboration (ATTC) allocation to aspirin increased the incidence of gastrointestinal haemorrhage or other serious extracranial bleed (usually defined as requiring transfusion or resulting in death) from 0.07% per year to 0.1% per year (HR=1.54, 95% CI 1.30-1.82).[65] The increase was only observed for non-fatal bleeds and there were fewer fatal bleeds in participants allocated aspirin compared with the controls. Haemorrhagic strokes (cranial bleeds) occurred at a rate of 0.04% per year compared with 0.03% in the control group. In these studies, aspirin doses ranged from 75-500mg daily. An earlier meta-analysis of 24 randomised trials (n=66,000) estimated that regular aspirin use (for an average of 28 months) increased the risk of gastrointestinal haemorrhage from 1.4% to 2.5% (odds ratio, OR=1.68, 95% CI 1.51-1.88).[66] A number of measures are known to reduce the risk of serious adverse events for those receiving aspirin[67] and these will be recommended in the trial. They include exclusion of patients with a high risk of complications (such as those with a previous ulcer or gastrointestinal bleed); careful management and treatment of symptoms such as dyspepsia; blood pressure monitoring; avoidance of concomitant non-steroidal anti-inflammatory drug (NSAID) use; and a low-dose option for elderly participants. *H.pylori* testing

and eradication will also be carried out and proton pump inhibitors (PPI) will be used where appropriate.

An assessment of the balance between the risks and benefits of aspirin use requires careful consideration of all its relevant effects. In particular, potential anti-cancer effects, cardiovascular outcomes and other health benefits must be balanced against serious toxicity. It has been suggested that the benefits of regular aspirin intake may outweigh the risks, even in average-risk populations and favour regular use of aspirin for primary prevention.[17, 37] In addition, any benefits of aspirin use are expected to rely on its regular and consistent use. Adherence is also expected to be better in a population who has recently undergone a cancer diagnosis and treatment. Whilst the participants in the CAPP2 study were younger than those expected to participate in Add-Aspirin, it is notable that there was no reported excess of adverse events in the aspirin arm, despite the dose of 600mg daily for 25 months (SD 12.5; range 0.8-60.6) and that, based on pill counts, adherence to therapy was good.[44, 68]

1.5 ASPIRIN DOSE

From current evidence, the optimal aspirin dose required to achieve anti-cancer effects is unclear. If the mechanism of action is via an effect on platelet function, then a dose of ≤100mg could be sufficient to observe a maximum effect on cancer outcomes. Evidence to support this comes from the meta-analysis data from cardiovascular trials where consistent anti-cancer effects were seen across trials evaluating low dose aspirin (75-100mg daily),[13, 37, 38] as well as the recent adjuvant epidemiological data from both the Netherlands and Scotland where effects of aspirin have been observed in cohorts in which the vast majority were taking a dose of 75-80mg daily.[15, 48] However, the mechanism of action underlying the anti-cancer effects of aspirin is unproven. It is plausible that there may be multiple mechanisms (which may differ for the effects on the spread and development of metastases compared to the development of a primary tumour) and that some or all of these could be dose–dependent. Data from the Nurses Health Study and HPFS indicate a possible dose effect since a larger impact on both colorectal and overall mortality in patients with a colorectal cancer diagnosis was seen for those taking the highest aspirin doses (>6 x 325mg tablets per week compared with 2-5 x 325mg per week).[23, 69] In the adjuvant setting where potential benefits of aspirin are large, a moderate increase in toxicity due to the use of a higher dose may be off-set by improvements in cancer outcomes. Whilst gastrointestinal toxicity is likely to increase with dose, the increase in toxicity associated with doses of up to 325mg compared with lower doses appears to be modest.[69, 70]

Given the above considerations, and in order to maximise the information that can be gained from the trial, Add-Aspirin will investigate use of both 100mg daily and 300mg daily aspirin compared with placebo. This increases the number of patients receiving a potentially active agent and addresses the dose issue, potentially saving many years of research time. For the primary analysis, for each cohort the aspirin arms will be combined and compared with placebo. Then, for tumour sites where an overall effect of aspirin is observed, the dose effect will be investigated in a combined analysis of the different disease site cohorts (for increased power). This design is highly efficient, addressing multiple research questions within a single study.

1.6 ONGOING STUDIES OF ASPIRIN AS A CANCER THERAPY

There is one similar ongoing trial worldwide. ASCOLT is a placebo-controlled, phase III trial, recruiting in Asia, which will assess the use of adjuvant aspirin (200mg daily for 3 years) for preventing

recurrence in colorectal cancer.[71] Add-Aspirin complements this study by addressing a similar research question in a cohort of Western colorectal cancer patients, but will additionally address the dose question and investigate the intervention in other disease sites. Add-Aspirin will not recruit colorectal cancer patients in Asia due to this potential conflict. Other ongoing trials which will provide information on aspirin use and cancer outcomes include: CAPP3, assessing use of lower doses of daily aspirin for prevention of cancers associated with Lynch syndrome; ASPREE, assessing overall health benefits of regular low-dose aspirin in the elderly;[72] ASCEND, assessing use of low-dose aspirin and omega-3 fatty acids for primary prevention of cardiovascular events in diabetics;[73] AspECT, assessing use of acid prevention with or without aspirin for reducing cancer risk in patients with Barrett's oesophagus;[74] and SeAFOod, assessing use of eicosapentaenoic acid with or without aspirin for the prevention of colorectal adenomas.[75]

Since aspirin is intended to be given in addition to standard primary therapy in Add-Aspirin, rather than replacing any element of current treatment, it will be important to include participants who have already taken part in other ongoing trials of primary treatments wherever possible (subject to agreement of the relevant trial teams and careful consideration of both the practical and statistical implications). This will allow assessment of the efficacy of aspirin in participants who have received both current and (potentially) future standard treatment, ensuring that the trial remains relevant.

1.7 POTENTIAL IMPACT OF THE TRIAL

The data summarised above strongly suggest that aspirin has the potential to have a significant effect in preventing the development and spread of cancer when the tumour burden is minimal. In the adjuvant setting therefore, given the high risk of disease recurrence and mortality, these potential benefits are expected to outweigh the risks associated with aspirin toxicity. Thus, this warrants further investigation in robust, well-designed studies. The recently published studies strengthen the rationale for this trial and have led to renewed interest about the potential of aspirin as an anti-cancer agent. The study fits well with other ongoing work investigating aspirin as an anti-cancer agent in a variety of settings.

If aspirin is shown to be beneficial as an adjuvant treatment, it would change practice. Aspirin is a low-cost, generic drug, available worldwide. Therefore, compared with many new agents or complex regimens, the intervention could be implemented quickly and on a broad scale, including in lower resource settings. As an inexpensive drug which could have a therapeutic role for several of the most common cancers, aspirin, even with a modest therapeutic effect, could potentially have a huge impact on the global cancer burden, particularly given the increasing cancer incidence in lower resource countries.

1.8 OBJECTIVE

Add-Aspirin aims to assess whether regular aspirin use after standard therapy, including surgery and neo-adjuvant/adjuvant chemotherapy and/or radiotherapy, can prevent recurrence and prolong survival in participants with common solid tumours. Multicentre and international recruitment will allow assessment of the intervention in a range of settings, with the aim of demonstrating that implementation is both feasible and cost-effective. A secondary aim is to assess the potential overall health benefits of aspirin for these participants.

2 SELECTION OF CENTRES/CLINICIANS

The trial sponsor in the UK, University College London (UCL), has overall responsibility for centre and Investigator selection. The trial is run and managed by the MRC CTU with some operational roles delegated to the Tata Memorial Hospital and a Clinical Research Organisation (CRO) in India.

2.1 CENTRE AND INVESTIGATOR INCLUSION CRITERIA

Those centres that meet the criteria in section 2.1.3 – 2.1.5 will be issued with the Add-Aspirin master file documentation for their Site-Specific Approval (SSA) or other local approvals as required and Add-Aspirin accreditation documents. Centres must complete Add-Aspirin accreditation documents at the same time as applying for their local approval.

Centres will be from the UK initially, with additional centres in India joining shortly afterwards. Other countries may join one or all of the tumour site-specific cohorts subject to resource and organisational considerations, and assessment of individual centres.

2.1.1 PRINCIPAL INVESTIGATORS (PI) AND CO-PIS

Centres may enter participants in one, some or all, of the tumour site-specific cohorts. Participation in all the tumour site-specific cohorts will be encouraged and for each a named co-PI with the relevant clinical expertise will be required. For the purposes of regulatory and ethics applications and approvals, only one PI should be named per centre. Hereafter, the term “Investigators” will be used where the statement is applicable to both the PIs and co-PIs.

2.1.2 INDIAN CENTRES

Initial Indian participating centres have been selected prior to trial commencement. Further centres may be selected based on similar criteria to sections 2.1.3 – 2.1.5 and the required documents must be completed. Indian centres will also be assessed by the CRO to ensure resources are adequate.

2.1.3 INVESTIGATORS QUALIFICATIONS AND AGREEMENTS

To participate in the Add-Aspirin trial, the Investigators and clinical trial centres must fulfil a set of basic criteria that have been agreed by the Add-Aspirin Trial Management Group (TMG) and are defined below.

1. The Investigators should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial at their centre. PIs should provide an up-to-date curriculum vitae as evidence of such qualifications and confirm other centre personnel are suitably qualified on the Investigator Statement.

2. The Investigators should be familiar with the investigational product, as described in the protocol, the product information and other information sources provided by the Sponsor and be prepared to seek additional specialist advice where appropriate.

3. The Investigators should be aware of, and should comply with, the principles of Good Clinical Practice (GCP) and the applicable regulatory requirements. A record of GCP training should be accessible for all Investigators.

4. The Investigators and centre should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).

5. Delegation logs of appropriately-qualified persons for each cohort, to whom the PI or co-PI has delegated significant trial-related duties should be maintained.

6. PIs and co-PIs should sign an Investigator Statement, which verifies that the centre is willing and able to comply with the requirements of the trial.

2.1.4 ADEQUATE RESOURCES

1. The Investigators should be able to demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period (between 3-6 years depending on tumour site), that is, the Investigators regularly treat the target population and that potential participants are discussed in regular Multiple Disciplinary Team (MDT) meetings.

2. The Investigators should have sufficient time to properly conduct and complete the trial within the agreed trial period.

3. The Investigators should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

4. The Investigators should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

5. The centre should have sufficient data management resources to ensure prompt data return.

2.1.5 CENTRE ASSESSMENT

Each selected centre must complete the Add-Aspirin accreditation documents, which includes the Investigator Statement, Signature and Delegation of Responsibilities Log, and staff contact details. The Investigator Statement verifies that the centre is willing, and able to comply with the requirements of the trial. This will be signed by the PI at the centre. In addition, and in compliance with the principles of GCP, all centre staff participating in the trial must complete the Signature and Delegation of Responsibilities Log and forward this to the MRC CTU. The MRC CTU must be notified of any changes to trial personnel and/or their responsibilities. An up-to-date copy of this log must be stored in the Trial Master File (TMF) at the centre and also at the MRC CTU or CRO.

2.2 APPROVAL AND ACTIVATION

The regulatory authorities require that the names and addresses of all participating centre PIs are provided. MRC CTU will perform this task for UK centres; hence it is vital to receive full contact details for all PIs prior to their entering participants.

On receipt of the required documents and approvals at the MRC CTU, confirmation of activation will be provided to the centre. The centre's pharmacist will also be informed of the centre's activation and an initial drug order will be dispatched to the named pharmacist in the accreditation documents. Trial participants cannot be entered into Add-Aspirin until the centre is notified of its activation.

The centre should conduct the trial in compliance with the protocol as agreed by the sponsor and by the regulatory authority(ies), and which was given favourable opinion by the Research Ethics Committee (REC) and/or Institutional Review Board (IRB).

A list of activated centres may be obtained by contacting the Trial Managers at MRC CTU.

3 SELECTION OF PARTICIPANTS

Providing potential participants with trial information (see Participant Information Sheet, appendix I) at the earliest opportunity following or during their primary therapy will allow time for them to consider their participation and for any queries or issues surrounding eligibility to be addressed. This will ensure appropriate enrolment and optimal trial recruitment. Participants should be enrolled as soon as it is considered clinically safe to do so (see section 4.2). For most cohorts we would expect this to be whilst their adjuvant therapy is ongoing.

There will be no exceptions to eligibility requirements at the time of registration and randomisation. Participants will be considered eligible for enrolment if they fulfil all the inclusion criteria and none of the exclusion criteria as defined in the following sections. Eligibility should be assessed at registration and those not meeting the criteria should not join the study. After the run-in period, participants will be assessed to ensure suitability for the study prior to randomisation.

It is accepted that there may be some variability of timing within the clinical practice of investigations and procedures so any queries regarding potential participants whose investigations may be outside of the timelines in section 3, should be discussed with the Trial Managers at the MRC CTU. All questions about eligibility criteria should be addressed **prior to** attempting to register or randomise the participant by contacting the Trial Managers at the MRC CTU in the UK by telephone or email or the trial co-ordinator in India.

Inclusion and exclusion criteria are presented separately for each tumour site cohort.

Please note that the trial eligibility criteria are designed such that those who would have an increased risk of serious toxicity from aspirin are excluded, but Investigators should also exercise clinical judgement in identifying potential participants who may be unsuitable for participation in the trial.

3.1 BREAST COHORT INCLUSION CRITERIA

1. Men or women with histologically confirmed invasive breast cancer.
2. Patients have undergone complete primary invasive tumour excision with clear margins as judged by the multidisciplinary team.
3. Surgical staging of the axilla must have been undertaken by sentinel node biopsy, axillary sampling or dissection.
4. In those patients with a positive sentinel node biopsy:
    a. If 1, 2 or 3 nodes are positive, subsequent management of the axilla (with surgery, radiotherapy or no further intervention) should follow institutional policy, and be completed prior to registration.
    b. If 4 or more nodes are involved, patients must have undergone completion axillary node dissection.
5. Radiotherapy:
    a. Patients who have undergone breast-conserving surgery should receive adjuvant radiotherapy.
    b. Patients who have undergone mastectomy should receive radiotherapy if they have more than 3 axillary lymph nodes involved.
    c. Patients who have undergone mastectomy and have T3 tumours and/or 1, 2 or 3 involved lymph nodes may (or not) receive radiation as per institutional practice.
6. Final histology must fall within at least one of these three groups:
    a. Node positive
    b. Node negative with high-risk features, defined as two or more of:
        - ER negative (Allred score <3/8 or negative according to institutional criteria)
        - HER2 positive
        - Grade 3
        - Lymphovascular invasion present
        - Age less than 35
        - Oncotype Dx score of >25

    In the above definitions patients with micrometastases should be regarded as node positive. Patients with isolated tumour cells should be regarded as node negative.
    c. Patients who have received neo-adjuvant chemotherapy and have both:
        - A hormone receptor negative/HER2 negative tumour, a HER2 positive tumour or a hormone receptor positive grade 3 tumour, and,
        - Did not achieve a pathological complete response with neoadjuvant systemic therapy (defined as no invasive cancer on H&E evaluation of the resected breast specimen and all sampled ipsilateral axillary lymph nodes).
7. Patients who received standard neo-adjuvant and/or adjuvant chemotherapy or radiotherapy are eligible. Timing of trial registration in terms of the treatment pathway should be as described in section 4.2. (For confirmation of standard therapy, please contact MRC CTU).
8. Known HER2 and ER status.
9. No clinical or radiological evidence of residual or distant disease according to routine practice staging tests.
10. Participants may receive endocrine therapy and trastuzumab according to standard practice concomitant with trial participation. All participants with ER positive disease should be planned to undergo a minimum of 5 years of adjuvant endocrine therapy using standard agents or as part of an agreed trial.
11. Patients who are already participating (or have participated) in other primary treatment trials may be eligible but this must be agreed in advance with the relevant trial teams. Trials where there is already an agreement in place are listed in section 4.4.1. If a potential

participant is enrolled in a trial that is not listed, this should be discussed with the MRC CTU prior to registration.
12. WHO performance status 0, 1 or 2.
13. Written informed consent.

3.2 BREAST COHORT EXCLUSION CRITERIA

1. Metastatic or bilateral breast cancer.
2. Current or previous regular use of aspirin (at any dose) or current use of another NSAID for any indication (see appendix IV for list of medications not permitted in the trial).
   Regular aspirin use is defined as taking aspirin more than twice in any given week for more than 4 consecutive weeks.
   Current NSAID use is defined as taking any NSAID for more than a week in the preceding month. If investigators feel that this definition may unfairly exclude a participant, this can be discussed with the MRC CTU and a case by case decision will be made.
3. A past history of adverse reaction or hypersensitivity to NSAIDs, celecoxib, aspirin or other salicylates or sulphonamides, including asthma, that is exacerbated by use of NSAIDs.
4. Current use of anti-coagulants.
5. Current or long-term use of oral corticosteroids. The treating physician should make the clinical decision whether a patient has been exposed to long-term therapy.
6. Active or previous peptic ulceration or gastrointestinal bleeding within the last year, except where the cause of the bleeding has been surgically removed.
7. Active or previous history of inflammatory bowel disease.
8. History of moderate or severe renal impairment, with eGFR<45ml/min/1.73m^2.
9. Previous invasive or non-invasive malignancy except:
   a. DCIS where treatment consisted of resection alone.
   b. Cervical carcinoma in situ where treatment consisted of resection alone.
   c. Basal cell carcinoma where treatment consisted of resection alone or radiotherapy.
   d. Superficial bladder carcinoma where treatment consisted of resection alone.
   e. Other cancers where the patient has been disease-free for ≥15 years.
10. Any other physical condition which is associated with increased risk of aspirin-related morbidity or, in the opinion of the Investigator, makes the patient unsuitable for the trial, including but not limited to severe asthma, haemophilia and other bleeding diatheses, macular degeneration and patients with a high risk of mortality from another cause within the trial treatment period.
11. Known glucose-6-phosphate dehydrogenase (G6PD) deficiency.
12. Known lactose intolerance.
13. LFTs greater than 1.5x the upper limit of normal unless the participant has been discussed with the MRC CTU and the Trial Management Group (TMG) agrees that they are suitable for the trial. This will be decided on a case-by-case basis.
14. Anticipated difficulties in complying with trial treatment or follow-up schedules.
15. <16 years old in the UK or <18 years old in India.
16. Participants in other treatment trials where this has not been agreed in advance by both trial teams. Specific trials where a second randomisation has already been agreed with the relevant trial teams are indicated in section 4.4.1. For all other trials, this should be discussed with the Trial Managers at the MRC CTU in the first instance.
17. Pregnant or breast feeding, or intending to become pregnant or breast feed during the trial treatment period. Participants should agree to inform the trial team if they subsequently become pregnant, or plan to become pregnant, whilst they are still receiving treatment in the trial (see section 5.4.4).

3.3 COLORECTAL COHORT INCLUSION CRITERIA

1. Histologically confirmed stage II or stage III (see appendix VII) adenocarcinoma of the colon or rectum and patients who have undergone resection of liver metastases with clear margins and no residual metastatic disease.
2. Patients with synchronous tumours if one of the tumours is at least stage II or III.
3. Serum CEA ideally ≤1.5 x upper limit of normal (ULN). Participants outside of this range can be discussed with the MRC CTU on an individual basis.
4. Have undergone curative (R0) resection with clear margins (margins ≥1mm or as judged by the multidisciplinary team).
5. Patients who have received standard neo-adjuvant and/or adjuvant treatment or therapy within an agreed trial. Timing of trial registration in terms of the treatment pathway should be as described in section 4.2. (For confirmation of standard therapy, please contact MRC CTU).
6. No clinical or radiological evidence of residual or distant disease according to routine practice staging tests.
7. Patients with known Lynch Syndrome are eligible, however CAPP3 trial should be offered in preference to Add-Aspirin if available. Patients that are not eligible for CAPP3 and patients that decline CAPP3 can be offered Add-Aspirin.
8. Patients who are already participating (or have participated) in other primary treatment trials may be eligible but this must be agreed in advance with the relevant trial teams. Trials where there is already an agreement in place are listed below in section 4.4.2. If a potential participant is enrolled in a trial that is not listed, this should be discussed with the MRC CTU prior to registration.
9. WHO performance status 0, 1 or 2.
10. Written informed consent.

3.4 COLORECTAL COHORT EXCLUSION CRITERIA

1. Proven (or clinically suspected) metastatic disease (patients who have undergone resection of liver metastases with clear margins and no residual metastatic disease are eligible).
2. Current or previous regular use of aspirin (at any dose) or current use of another NSAID for any indication (see appendix IV for list of medications not permitted in the trial).
   Regular aspirin use is defined as taking aspirin more than twice in any given week for more than 4 consecutive weeks.
   Current NSAID use is defined as taking any NSAID for more than a week in the preceding month. If investigators feel that this definition may unfairly exclude a participant, this can be discussed with the MRC CTU and a case by case decision will be made.
3. A past history of adverse reaction/hypersensitivity to NSAIDs, celecoxib, aspirin or other salicylates or sulphonamides, including asthma that is exacerbated by use of NSAIDs.
4. Current use of anti-coagulants.
5. Current or long-term use of oral corticosteroids. The treating physician should make the clinical decision whether a patient has been exposed to long-term therapy.
6. Active or previous peptic ulceration or gastrointestinal bleeding within the last year, except where the cause of the bleeding has been surgically removed.
7. Active or previous history of inflammatory bowel disease.
8. History of moderate or severe renal impairment, with eGFR<45ml/min/1.73m^2.
9. Previous invasive or non-invasive malignancy except:
   a. DCIS where treatment consisted of resection alone.
   b. Cervical carcinoma in situ where treatment consisted of resection alone.

c. Basal cell carcinoma where treatment consisted of resection alone or radiotherapy.
d. Superficial bladder carcinoma where treatment consisted of resection alone.
e. Other cancers where the patient has been disease-free for ≥15 years.

10. Any other physical condition which is associated with increased risk of aspirin-related morbidity or, in the opinion of the Investigator, makes the patient unsuitable for the trial, including but not limited to severe asthma, haemophilia and other bleeding diatheses, macular degeneration and patients with a high risk of mortality from another cause within the trial treatment period.
11. Known G6PD deficiency.
12. Known lactose intolerance.
13. LFTs greater than 1.5x the upper limit of normal unless the participant has been discussed with the MRC CTU and the TMG agrees that they are suitable for the trial. This will be decided on a case-by-case basis.
14. Anticipated difficulties in complying with trial treatment or follow-up schedules.
15. <16 years old in the UK or <18 years old in India.
16. Participants in other treatment trials where this has not been agreed in advance by both trial teams. Specific trials where a second randomisation has already been agreed with the relevant trial teams are indicated in section 4.4.2. For all other trials, this should be discussed with the Trial Managers at the MRC CTU in the first instance.
17. Pregnant or breast feeding, or intending to become pregnant or breast feed during the trial treatment period. Participants should agree to inform the trial team if they subsequently become pregnant, or plan to become pregnant, whilst they are still receiving treatment in the trial (see section 5.4.4).

3.5 GASTRO-OESOPHAGEAL COHORT INCLUSION CRITERIA

1. Patients with histologically confirmed adenocarcinoma, adenosquamous carcinoma or squamous cell cancer of the oesophagus, gastro-oesophageal junction or stomach.
2. Have undergone curative (R0) resection with clear margins (margin ≥1mm or as judged by the multidisciplinary team) or primary chemoradiotherapy given with curative intent.
3. Patients who have received standard neo-adjuvant and/or adjuvant treatment or therapy within an agreed trial are eligible. Timing of trial registration in terms of the treatment pathway should be as described in section 4.2. (For confirmation of standard therapy, please contact MRC CTU).
4. No clinical or radiological evidence of residual or distant disease according to routine practice staging tests.
5. Those who have undergone a partial gastrectomy or oesophagectomy should be prescribed a proton pump inhibitor for the duration of the trial where no contraindication exists.
6. Patients who are already participating (or have participated) in other primary treatment trials may be eligible but this must be agreed in advance with the relevant trial teams. Trials where there is already an agreement in place are listed in section 4.4.3. If a potential participant is enrolled in a trial that is not listed, this should be discussed with the MRC CTU prior to registration.
7. WHO performance status 0, 1 or 2.
8. Written informed consent.

3.6 GASTRO-OESOPHAGEAL COHORT EXCLUSION CRITERIA

1. Proven (or clinically suspected) metastatic disease.
2. Current or previous regular use of aspirin (at any dose) or current use of another NSAID for any indication (see appendix IV for list of medications not permitted in the trial).
   Regular aspirin use is defined as taking aspirin more than twice in any given week for more than 4 consecutive weeks.
   Current NSAID use is defined as taking any NSAID for more than a week in the preceding month. If investigators feel that this definition may unfairly exclude a participant, this can be discussed with the MRC CTU and a case by case decision will be made.
3. A past history of adverse reaction/hypersensitivity to NSAIDs, celecoxib, aspirin or other salicylates or sulphonamides, including asthma that is exacerbated by use of NSAIDs.
4. Current use of anti-coagulants.
5. Current or long-term use of oral corticosteroids. The treating physician should make the clinical decision whether a patient has been exposed to long-term therapy.
6. Active or previous peptic ulceration or gastrointestinal bleeding within the last year, except where the cause of the bleeding has been surgically removed.
7. Active or previous history of inflammatory bowel disease.
8. History of moderate or severe renal impairment, with eGFR<45ml/min/1.73m^2.
9. Previous invasive or non-invasive malignancy except:
   a. DCIS where treatment consisted of resection alone.
   b. Cervical carcinoma in situ where treatment consisted of resection alone.
   c. Basal cell carcinoma where treatment consisted of resection alone or radiotherapy.
   d. Superficial bladder carcinoma where treatment consisted of resection alone.
   e. Other cancers where the patient has been disease-free for ≥15 years.
10. Any other physical condition which is associated with increased risk of aspirin-related morbidity or, in the opinion of the Investigator, makes the patient unsuitable for the trial, including but not limited to severe asthma, haemophilia and other bleeding diatheses,

macular degeneration and patients with a high risk of mortality from another cause within the trial treatment period.

11. Known G6PD deficiency.
12. Known lactose intolerance.
13. LFTs greater than 1.5x the upper limit of normal unless the participant has been discussed with the MRC CTU and the TMG agrees that they are suitable for the trial. This will be decided on a case-by-case basis.
14. Anticipated difficulties in complying with trial treatment or follow-up schedules.
15. <16 years old in the UK or <18 years old in India.
16. Participants in other treatment trials where this has not been agreed in advance by both trial teams. Specific trials where a second randomisation has already been agreed with the relevant trial teams are indicated in section 4.4.3. For all other trials, this should be discussed with the Trial Managers at the MRC CTU in the first instance.
17. Pregnant or breast feeding, or intending to become pregnant or breast feed during the trial treatment period. Participants should agree to inform the trial team if they subsequently become pregnant, or plan to become pregnant, whilst they are still receiving treatment in the trial (see section 5.4.4).

3.7 PROSTATE COHORT INCLUSION CRITERIA

1. Men with histologically confirmed, node negative, non-metastatic adenocarcinoma of the prostate (T1-3a, N0). See appendix X for TNM staging definitions.
2. Have undergone curative treatment, either
    a. Radical prostatectomy.
    b. Radical radiotherapy (external beam or brachytherapy).
    c. Salvage radiotherapy following a rise in PSA after radical prostatectomy.
3. **Intermediate** or **high** risk according to D'Amico classification[76] (prior to radical treatment, see table 3).

Table 3. D'Amico Classification[76]

RISK CLASSIFICATION	
Low	▪ PSA less than or equal to 10 ▪ **And** Gleason score less than or equal to 6 ▪ **Or** clinical stage T1-2a
Intermediate	▪ PSA between 10 and 20 ▪ **Or** Gleason score of 7 ▪ **Or** clinical stage T2b
High	▪ PSA more than 20 ▪ **Or** Gleason score equal or larger than 8 ▪ **Or** clinical stage T2c-3a

4. WHO performance status 0, 1 or 2.
5. Written informed consent.

Depending on the curative treatment pathway, participants must additionally satisfy the following:

(a) Prostatectomy patients

6. Open, laparoscopic or robotic radical prostatectomy.
7. Men treated with immediate adjuvant radiotherapy are eligible. Timing of trial registration in terms of the treatment pathway should be as described in section 4.2.
8. Men receiving adjuvant hormone therapy (LHRH agonists, LHRH antagonists, bicalutamide monotherapy), planned for a maximum duration of three years, are eligible. Treatment can be ongoing at the time of registration/randomisation to Add-Aspirin.
9. Men randomised to any of the 3 arms of RADICALS Hormone Duration study (RADICALS-HD, ISRCTN 40814031) are eligible provided all other eligibility criteria are met.

(b) Radical radiotherapy patients

10. Men receiving neo-adjuvant and/or adjuvant hormone therapy (LHRH agonists, LHRH antagonists, bicalutamide monotherapy) planned for a maximum duration of three years are eligible, and this treatment may be ongoing at the time of registration in Add-Aspirin.
11. Timing of registration in Add-Aspirin in terms of the treatment pathway should be as described in section 4.2.

(c) Salvage radiotherapy patients (following rise in PSA after previous radical prostatectomy)

12. Men treated with salvage radiotherapy following a rise in PSA are eligible. Timing of trial registration in terms of the treatment pathway should be as described in section 4.2.
13. Men receiving neo-adjuvant and/or adjuvant hormone therapy (LHRH agonists, LHRH antagonists, bicalutamide monotherapy) planned for a maximum duration of three years are eligible, and this treatment may be ongoing at the time of registration in Add-Aspirin.

14. Men randomised to any of the 3 arms of RADICALS Hormone Duration study (RADICALS-HD, ISRCTN 40814031) are eligible provided all other eligibility criteria are met.

3.8 PROSTATE COHORT EXCLUSION CRITERIA

1. Biopsy proven or radiologically suspected nodal involvement or distant metastases from prostate cancer.
2. Adjuvant hormone therapy planned for >3 years.
3. Bilateral orchidectomy.
4. Current or previous regular use of aspirin (at any dose) or current use of another NSAID for any indication (see appendix IV for list of medications not permitted in the trial).
   Regular aspirin use is defined as taking aspirin more than twice in any given week for more than 4 consecutive weeks.
   Current NSAID use is defined as taking any NSAID for more than a week in the preceding month. If investigators feel that this definition may unfairly exclude a participant, this can be discussed with the MRC CTU and a case by case decision will be made.
5. A past history of adverse reaction/hypersensitivity to NSAIDs, celecoxib, aspirin or other salicylates or sulphonamides, including asthma that is exacerbated by use of NSAIDs.
6. Current use of anti-coagulants.
7. Current or long-term use of oral corticosteroids. The treating physician should make the clinical decision whether a patient has been exposed to long-term therapy.
8. Active or previous peptic ulceration or gastrointestinal bleeding, except where the cause of the bleeding has been surgically removed.
9. Active or previous history of inflammatory bowel disease.
10. History of moderate or severe renal impairment, with eGFR<45ml/min/1.73m^2.
11. Previous invasive or non-invasive malignancy except:
    a. Prostate cancer initially treated with prostatectomy and now being treated with salvage radiotherapy following a rise in PSA.
    b. Basal cell carcinoma where treatment consisted of resection alone or radiotherapy.
    c. Low grade superficial bladder carcinoma where treatment consisted of endoscopic resection alone.
    d. Other cancers where the patient has been disease-free for ≥15 years.
12. Any other physical condition which is associated with increased risk of aspirin-related morbidity or, in the opinion of the Investigator, makes the patient unsuitable for the trial, including but not limited to severe asthma, haemophilia and other bleeding diatheses, macular degeneration and patients with a high risk of mortality from another cause within the trial treatment period.
13. Known G6PD deficiency.
14. Known lactose intolerance.
15. LFTs greater than 1.5x the upper limit of normal unless the participant has been discussed with the MRC CTU and the TMG agrees that they are suitable for the trial. This will be decided on a case-by-case basis.
16. Anticipated difficulties in complying with trial treatment or follow-up schedules.
17. <16 years old in the UK or <18 years old in India.
18. Participants in other treatment trials where this has not been agreed in advance by both trial teams. Specific trials where a second randomisation has already been agreed with the relevant trial teams are indicated in the inclusion criteria. For all other trials, this should be discussed with the Trial Managers at the MRC CTU in the first instance.

3.9 NUMBER OF PARTICIPANTS

The target randomisation figure is 9,920 participants in the UK and India. Assuming that approximately 10% of participants will not be randomised following the run-in (for reasons relating either to toxicity or adherence), it is expected that 11,000 participants will be registered. Details of the number of participants expected to be recruited in each tumour site-specific cohort and the sample size calculations can be found in section 10.4.

3.10 PROCEDURES & INVESTIGATIONS PRIOR TO REGISTRATION AND RANDOMISATION

3.10.1 INFORMED CONSENT PROCEDURES

Prior to registration, written informed consent to enter into the trial must be obtained from participants. This should be done once they have had adequate time to read the Participant Information Sheet (PIS) (see Participant Information Sheet - appendix I), after explanation of the aims, methods, potential benefits and hazards of the trial and **before** any trial-specific procedures are performed, any blood samples are taken for the trial or any trial tablets are dispensed (see Consent Form – appendix II). This can be carried out by the Investigator or Research Nurse. Following successful completion of the run-in period (see section 4.1), and prior to randomisation, the participant should be asked to re-confirm their consent to participate and be randomised in the main trial on the original consent form.

Throughout the consent process, it must be made completely and unambiguously clear that the participant is able to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting their treatment. The importance of allowing continued collection of data wherever possible, in order to allow the participant's experiences, positive or negative, to be reflected in the trial data, should however be emphasised.

Signed consent forms must be kept by the Investigators, a copy sent to the MRC CTU and a copy given to the participant. A letter should be sent to the general practitioner (GP) informing him/her of the trial and the participant's involvement in it (see GP Letter – appendix III) once they have been registered.

3.10.2 SCREENING PROCEDURES AND INVESTIGATIONS

Any trial-specific assessments required to confirm a participant's eligibility should be carried out prior to registration, and after informed consent is given.

Following the run-in period of approximately 8 weeks, registered participants should be assessed with regard to their demonstrated adherence and tolerance during the run-in period to confirm whether they are still suitable for randomisation.

Please refer to the Trial Assessment Schedule (see page xi -xiv) and section 6.2 for details of assessments required to be carried out and timings of assessments.

4 REGISTRATION AND RANDOMISATION

REGISTER PARTICIPANTS ONLINE AT:
www.addaspirintrial.org

RANDOMISE PARTICIPANTS BY PHONE:
UK: +44 (0)20 7670 4777 (Mon – Fri, 09:00-17:00 UK time)
India: Details will be confirmed

Email (for all registration or randomisation queries): mrcctu.add-aspirin@ucl.ac.uk

Add-Aspirin is a multi-centre trial for participants who have undergone primary treatment with curative intent for a non-metastatic common solid tumour. There are four parallel cohorts for patients who have been diagnosed and treated for breast, colorectal, gastro-oesophageal or prostate cancer. Participants will be randomised to 100mg aspirin, 300mg aspirin or placebo. For the purposes of blinding, a matching placebo (100mg aspirin placebo or 300mg aspirin placebo), will be taken daily in the placebo group. Participants ≥75 years old will only be randomised to 100mg aspirin or placebo.

4.1 REGISTRATION AND RUN-IN PERIOD

Participants that meet all the inclusion criteria and none of the exclusion criteria for their cohort and wish to participate, should sign the Add-Aspirin consent form. These participants will then be registered via the trial website and assigned a participant identification number.

All participants will be required to complete an active run-in period after registration but prior to randomisation where they will take 100mg aspirin daily (one tablet per day) open-label, for a period of approximately 8 weeks. At the end of this run-in period, the participant's tolerance of aspirin and adherence to daily treatment will be assessed (see section 6.2). Those participants identified as suitable for further study participation, and who remain eligible and are willing to continue in the trial should then re-confirm their consent to participate (see section 3.10) before being randomised.

Those who do not go on to be randomised in the trial will be asked whether they consent to donate an additional blood sample and their active participation in the trial will then end at this time. However, passive follow-up will continue via routinely-collected healthcare datasets, if they have given consent for this (see section 9.3.1). This approach will allow those individuals who are unlikely to be able to tolerate aspirin, as well as those who are unlikely to be able to adhere to the protocol treatment schedule, to be identified. See section 5.1 and section 6.2 for further details on the run-in period treatment and assessments at the end of the run-in period.

4.2 TIMING OF INITIATION OF THE RUN-IN PERIOD WITHIN THE CANCER TREATMENT PATHWAY

The following are given as guidelines for when the active run-in period can be started, though potential participants can be given information about the trial before this.

Following definitive surgery, if no adjuvant chemotherapy or radiotherapy is planned there should be a gap of at least 6 weeks, but no more than 12 weeks, between surgery and starting the run-in period.

If adjuvant chemotherapy is planned, in the colorectal and gastro-oesophageal cohorts the run-in period can be started after 6 weeks of chemotherapy providing that the platelet count on day 1 of the preceding chemotherapy cycles is $\geq 100 \times 10^9$/L. In the breast cohort, adjuvant chemotherapy should be completed before the run-in period is started. In all cohorts, the run-in treatment should be started no later than 6 weeks after the end of planned chemotherapy.

In general, the run-in period can be started during adjuvant radiotherapy alone, but should be started at least 6 weeks after definitive surgery and no later than 6 weeks after the last fraction.

If definitive radiation or chemoradiation is the primary therapy (prostate and gastro-oesophageal), the run-in period can start as soon as this is complete and no later than 12 weeks after the last fraction of radiotherapy.

If the potential participant has received treatment as part of another trial, please see section 4.4.

Examples of likely clinical scenarios are given below. For other clinical scenarios please direct queries to the MRC CTU.

4.2.1 BREAST COHORT

For these participants, hormone therapy and/or trastuzumab may be planned or ongoing.

a) **Surgery and no adjuvant chemotherapy or radiotherapy planned:** the run-in period can start between 6 and 12 weeks after definitive surgery (defined as wide local excision or mastectomy).

b) **Surgery and adjuvant chemotherapy (no radiotherapy planned):** the run-in period should start after chemotherapy has been completed and no later than 6 weeks after the end of planned chemotherapy.

c) **Surgery and adjuvant radiotherapy (no chemotherapy planned):** the run-in period can start 6 weeks after surgery (radiotherapy may be ongoing) and no later than 6 weeks after the last fraction of radiotherapy.

d) **Surgery and adjuvant chemotherapy followed by adjuvant radiotherapy:** the run-in period should not be started until the chemotherapy has been completed and no later than 6 weeks after the final fraction of radiotherapy.

4.2.2 COLORECTAL COHORT

a) **Surgery and no adjuvant chemotherapy or radiotherapy planned** (but may have been preceded by chemotherapy or radiotherapy): the run-in period should start between 6 and 12 weeks after definitive surgery.

b) **Surgery and adjuvant chemotherapy (no radiotherapy planned):** the run-in period can start after 6 weeks of chemotherapy providing that the platelet count on day 1 of the preceding

chemotherapy cycles is ≥100 x 10^9/L. The run-in period should start no later than 6 weeks after the end of planned chemotherapy.

c) **Surgery and adjuvant radiotherapy (no chemotherapy planned):** the run-in period can start 6 weeks after surgery (radiotherapy may be ongoing) and no later than 6 weeks after the last fraction of radiotherapy.

d) **Surgery and adjuvant chemotherapy followed by adjuvant radiotherapy:** the run-in period can start after 6 weeks of chemotherapy providing platelet counts as defined in (b) above. The run-in period should start no later than 6 weeks after the last fraction of radiotherapy.

4.2.3 GASTRO-OESOPHAGEAL COHORT

a) **Surgery and no adjuvant chemotherapy or radiotherapy planned (but may have been preceded by chemotherapy):** the run-in period should start between 6 and 12 weeks after definitive surgery.

b) **Surgery and adjuvant chemotherapy:** the run-in period can start after 6 weeks of chemotherapy providing that the platelet count on day 1 of the preceding chemotherapy cycles is ≥100 x 10^9/L. The run-in period should start no later than 6 weeks after the end of planned chemotherapy.

c) **Definitive chemoradiation:** the run-in period can start as soon as this is complete and no later than 12 weeks after the final fraction of radiotherapy.

4.2.4 PROSTATE COHORT

For these participants, hormone therapy may be planned or ongoing (for a maximum duration of 3 years).

a) **Prostatectomy and no adjuvant chemotherapy or radiotherapy planned:** the run-in period should start between 6 and 12 weeks after definitive surgery.

b) **Prostatectomy and adjuvant radiotherapy:** the run-in period should start at least 6 weeks after surgery and no later than 6 weeks after the last fraction of radiotherapy.

c) **Radical radiotherapy:** the run-in period can start as soon as this is complete and no later than 12 weeks after the final fraction of radiotherapy.

d) **Salvage radiotherapy following previous prostatectomy (irrespective of previous therapy):** the run-in period should start no later than 12 weeks after the final fraction of radiotherapy.

4.2.5 TOXICITY DURING ADJUVANT THERAPY

Where the run-in period is started while adjuvant chemotherapy and/or radiotherapy is ongoing, and poor tolerance is attributed to the ongoing adjuvant therapy, a further run-in period can be performed when adjuvant therapy is finished, providing that the further run-in commences no later

than 8 weeks from day 1 of the last cycle of chemotherapy or from the final fraction of radiotherapy.

4.3 RANDOMISATION PROCESS

Participants may be randomised if they meet all of the inclusion criteria and none of the exclusion criteria for their cohort, and are felt to be suitable for long-term treatment with daily aspirin following the run-in period (see section 5.1). The majority of participants (those <75 years) will be randomised (1:1:1) to either 100mg aspirin, 300mg aspirin, or matching placebo. Participants will have an equal chance of receiving 100mg aspirin, 300mg aspirin or a placebo. Participants ≥75 years will be randomised (2:1) between 100mg aspirin and matching placebo only. In all cases, neither the participant nor the investigator will be notified of the final treatment allocation (double-blind).

Further details of the methods used for treatment allocation can be found in section 10.1.

A manual randomisation process will be set up to cover any instances when the main electronic system is not working. If there are any problems for centres accessing the system, the Trial Managers at the MRC CTU should be contacted (see page v).

4.4 CO-ENROLMENT GUIDELINES

Since aspirin is intended to be given following or alongside standard primary therapy, rather than replacing any element of current treatment, it will be appropriate to include participants who have already taken part in trials of primary treatments wherever possible. This will allow assessment of the efficacy of aspirin in participants who have received both current and potentially future standard treatment. Participants in the trials listed below will be permitted to participate in Add-Aspirin (providing they satisfy all other eligibility criteria), and this has been agreed with the relevant trial teams. If they have participated in another trial, which is not listed here, please contact the MRC CTU to discuss this prior to their registration into Add-Aspirin.

Ideally, following entry into Add-Aspirin, if participants should wish to enter subsequent cancer treatment trials prior to a primary outcome event, please contact the Trial Manager to discuss this.

Participants in the following trials may enter Add-Aspirin (providing they satisfy all other eligibility criteria). Other trials may be added to this list after discussions between the Trial Management Groups. For the most up-to-date list, please contact the MRC CTU:

4.4.1 BREAST TRIALS

4.4.1.A UK Trials

Fast FORWARD (ISRCTN 19906132)
Persephone (ISRCTN 52968807)

4.4.1.B Indian Trials

Tata Memorial Hospital (TMH) trial of exercise in patients undergoing treatment for breast cancer (CTRI/2011/05/001749)
TMH trial of pre-operative trastuzumab
TMH trial of progesterone for preventing chemotherapy-induced neurotoxicity
TMH trial assessing blockage of voltage gate sodium channels during breast cancer surgery

4.4.2 COLORECTAL TRIALS

FOxTROT (ISRCTN 87163246)

4.4.3 GASTRO-OESOPHAGEAL TRIALS

4.4.3.A UK Trials

ST03 (ISRCTN 46020948)

4.4.3.B Indian Trials

TMH trial evaluating the role of radical lymphadenectomy
TMH trial of neo-adjuvant chemotherapy vs chemoradiotherapy

4.4.4 PROSTATE TRIAL

RADICALS-HD (Hormone Duration Randomisation) (ISRCTN 40814031 – see appendix XI)

5 TREATMENT OF PARTICIPANTS

5.1 TREATMENT DURING THE RUN-IN PERIOD

See section 4.2 for when the run-in period can commence. All participants will take 100mg aspirin (open-label) once daily for approximately 8 weeks prior to randomisation in order to identify those individuals who are unlikely to be able to tolerate aspirin and those who are unlikely to be able to adhere to the protocol treatment regimen. The guidance on investigating and managing treatment toxicity, provided in the subsequent sections, should be followed during the active run-in period as well as during randomised treatment in the trial, except that dose reductions will not be relevant during the run-in period and so treatment should be discontinued in the event of significant toxicity.

At the end of the run-in period, treatment adherence and toxicities will be assessed, as described in section 6.2, to identify those participants who are suitable to be randomised into the trial. Participants that experience any aspirin-related severe toxicity (defined as ≥grade 3 Common Terminology Criteria for Adverse Events (CTCAE v4)) or any grade of gastrointestinal bleeding, active gastrointestinal ulceration, tinnitus, macular degeneration, intracranial bleeding or hypersensitivity to aspirin should permanently discontinue aspirin immediately and will not be eligible for the trial.

As described in section 6.2, if the Investigator feels that the reason for inadequate adherence is temporary, the run-in period may be extended by 4 or 8 weeks to reassess adherence and toxicity. All extensions to the run-in period must be discussed with the Trial Manager and the trial medication will be resupplied accordingly.

No 'wash-out' period will be necessary between the run-in period and randomisation.

5.2 RANDOMISED TRIAL TREATMENT

Participants will self-administer one enteric-coated tablet of either 300mg aspirin, 100mg aspirin or matching placebo. This should be taken daily and swallowed whole with plenty of liquid (e.g. a glass of water) preferably after a meal. This should be continued for at least five years or until one of the primary outcome measures is met (see section 10.2). The risk of toxicity with aspirin increases with age and in order to reduce this risk those 75 years old or over will only be randomised to aspirin 100mg or matching placebo.

Participants and Investigators will be blinded to treatment allocation. Patient reported adherence to trial treatment will be collected during follow-up.

5.3 DISPENSING

Participating centres will be provided with a start-up supply of trial medication once the institution has been approved for participation in Add-Aspirin (see section 2). Packs of trial treatment will be labelled with a code to maintain blinding. Once received in the pharmacy, the drug should be kept in a dry, safe place according to the Summary of Product Characteristics (SPC). Trial-specific working practices will be supplied separately to the centre pharmacist in the pharmacy pack.

The trial medication must only be used to treat participants in the Add-Aspirin trial. Both the run-in period tablets and tablets for randomised patients should be taken from Add-Aspirin trial stock only.

Only the Investigator or a person assigned by them that has been appropriately trained and assigned on the delegation log to do so, will be allowed to prescribe the drug to the participant. Institutions will be given guidance on re-supply in the drug supply manual.

5.4 DOSE MODIFICATIONS, INTERUPTIONS & DISCONTINUATIONS

Aspirin is a licensed, generic drug which has been in use for many years and the safety profile is well documented. Rates of toxicity are low in comparison with other adjuvant therapies. Where appropriate, prophylactic measures can be used to reduce the risk of toxicity. Suggested management principles for events and toxicities during the trial can be found below. Toxicities will be graded using the CTCAE v4 (see appendix V) and the SPC can be consulted for further information.

5.4.1 POSSIBLE TOXIC EFFECTS

In order to avoid unblinding, wherever possible, Investigators should investigate and manage toxicities under the assumption that the participant is receiving 300mg aspirin. Possible toxicities as detailed in the SPC for Bayer aspirin tablets are as follows: (please note this list does not include all known toxicities.)

Table 4. Terminology used for the frequency of aspirin toxicities

Very common: ≥ 1/10 patients
Common: ≥ 1/100 to < 1/10 patients
Uncommon: ≥ 1/1,000 to < 1/100 patients
Rare: ≥ 1/10,000 to < 1/1,000 patients
Very rare: < 1/10,000 patients
Not known: frequency cannot be estimated from the available data

5.4.1.A Blood and lymphatic system disorders

Rare to very rare:

- Serious bleeding, such as cerebral bleeding, especially in patients with uncontrolled hypertension and/or concomitant treatment with anticoagulants, which in isolated cases may be potentially life-threatening, have been reported.
- Bleeding, e.g. nose bleeds, bleeding gums, cutaneous bleeding, menorrhagia or urogenital bleeding, possibly with prolongation of the bleeding time. This effect can persist for 4 to 8 days after use.

5.4.1.B Gastrointestinal disorders

Common:

- Gastrointestinal disorders such as dyspepsia (heartburn), nausea, vomiting, abdominal pain and diarrhoea.
- Minor blood loss from the gastrointestinal tract (microhaemorrhage).

Uncommon:

- Gastrointestinal ulcers which in very rare cases can lead to perforation.
- Gastrointestinal bleeding.
- Long-term use of aspirin may cause iron deficiency anaemia due to occult blood loss from the gastrointestinal tract.

Rare:

- Severe gastrointestinal haemorrhage (e.g. requiring hospital admission)

5.4.1.C Nervous system disorders

Rare:

- Intracranial haemorrhage.

Unknown:

- Headache, dizziness, vertigo, impaired hearing ability, tinnitus or mental confusion (these can be signs of an overdose).

5.4.1.D Skin and subcutaneous tissue disorders

Common:

- Increased risk of bruising

Uncommon:

- Urticaria.

Rare:

- Erythema nodosum.
- Erythema multiforme.
- Steven Johnson Syndrome.
- Toxic epidermal necrolysis.

5.4.1.E Immune system disorders

Rare:

- Hypersensitivity reactions of the skin, the respiratory tract and the gastrointestinal tract, particularly in asthma sufferers.
- Hypersensitivity reactions can lead to anaphylactic shock and angioedema.

5.4.1.F Hepatobiliary disorders

Very rare:

- Transient elevated liver enzymes.

Unknown:

- Hepatitis and hepatic insufficiency.

5.4.1.G Renal and urinary disorders

Very rare:

- Impaired kidney function.

5.4.1.H Metabolism

Very rare:

- Hypoglycaemia.

At low doses acetylsalicylic acid reduces the excretion of uric acid. Aspirin should be used with caution in patients with gout as this may worsen, or cause an acute exacerbation of gout.

5.4.1.I Eyes and vision

Unknown:

- Macular degeneration.

5.4.2 PROPHYLACTIC MEASURES

Eligibility criteria have been formulated so that individuals with an increased risk of serious toxicity from aspirin are excluded. This risk is further mitigated by limiting those 75 years old or over to

100mg of aspirin (or matching placebo) and restricting concomitant use of other medications that increase the risk of serious toxicity (see appendix IV).

The management of those experiencing dyspepsia during the trial is described in section 5.4.3.A. Patients experiencing dyspepsia prior to trial registration should undergo investigation and successful treatment (including *H.pylori* eradication where indicated) before enrolling in the Add-Aspirin trial. Investigators are referred to guidance on the management of dyspepsia from the UK National Institute for Health and Clinical Excellence (NICE, available from http://guidance.nice.org.uk/CG17/Guidance/pdf/English).[77] Smoking and regular use of alcohol are also known to increase the risk of dyspepsia and should be avoided.

For those who are asymptomatic, prophylactic measures to reduce the risk of gastrointestinal toxicity from aspirin, such as PPI prophylaxis and *H.pylori* eradication, are not routinely recommended in participants at low risk of GI complications and are not mandated in the Add-Aspirin protocol. However, PPI use for the duration of aspirin treatment is recommended for patients who have undergone oesophagectomy or partial gastrectomy and should also be considered for elderly patients (≥75 years), or any other participant who might be at increased risk of toxicity.

Intracranial bleeding is a rare toxicity of aspirin. Hypertension can increase the risk of an intracranial bleed. Those with poorly controlled hypertension should have their blood pressure management optimised to bring it within normal limits prior to enrolling in the trial and blood pressure should be monitored throughout the trial.

For those participants who are due to undergo elective surgery, they should discuss withholding their trial medication with their surgeon for a period of time. If unplanned surgery is needed, emergency unblinding is available where it would alter management (see section 5.6).

If a participant's platelet count falls below $50x10^9$/L, the trial treatment should be withheld until it recovers to above this level.

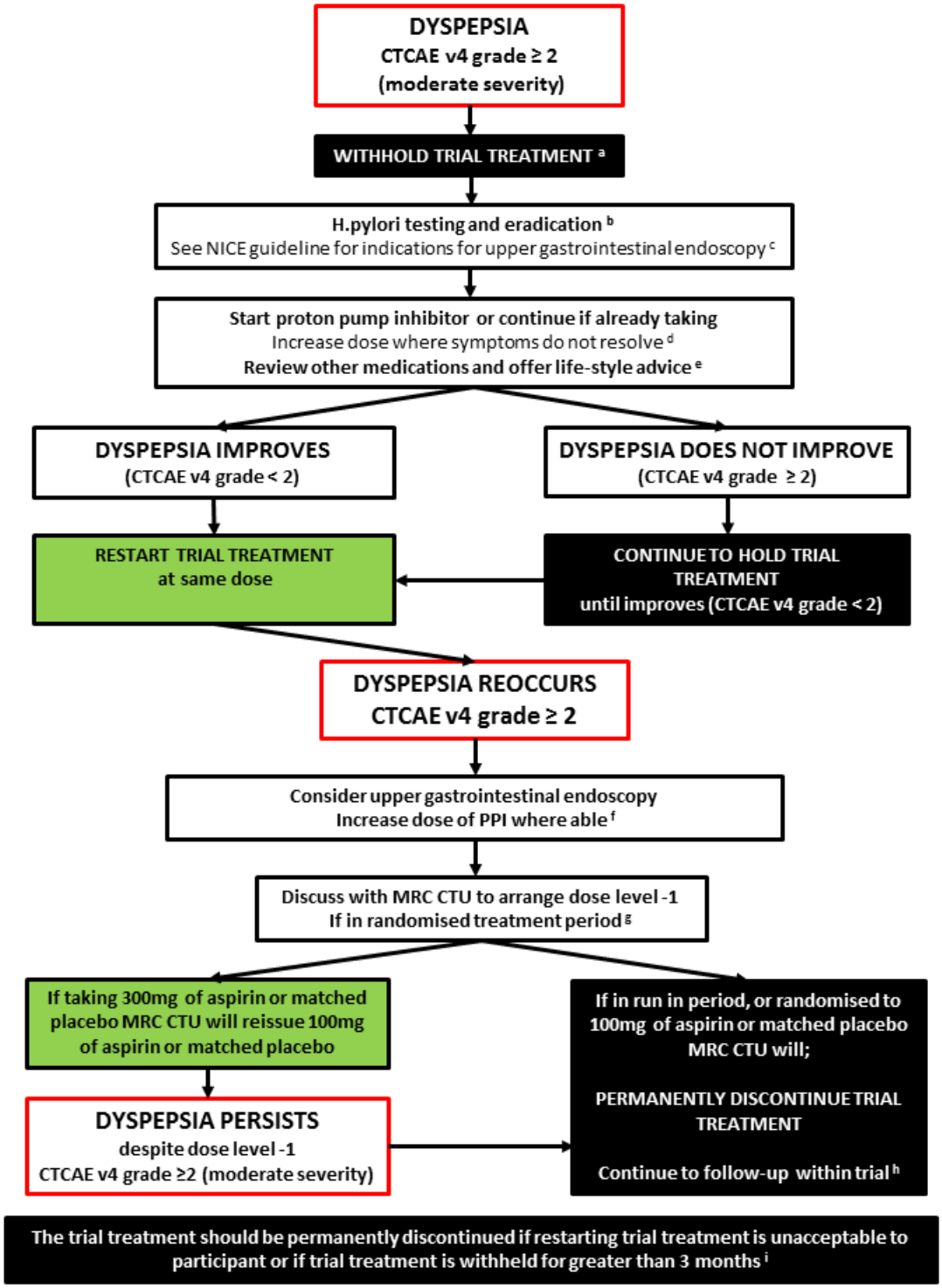
5.4.3 TOXICITY MANAGEMENT

Participants should be advised to immediately inform healthcare professionals if, at any time during the trial, they have a suspected heart attack, stroke, serious bleed or any other serious medical event and inform the treating healthcare professional that they are in the Add-Aspirin trial. In particular, criteria where urgent referral for endoscopy and suspension of trial treatment may be appropriate include chronic gastrointestinal bleeding (immediate referral if significant acute bleeding), progressive dysphagia, iron deficiency anaemia or persistent vomiting.[77]

5.4.3.A Management of Dyspepsia

Dyspepsia is characterised by discomfort in the upper abdomen, often described as heartburn, which can be associated with bloating and occasionally nausea and vomiting. Dyspepsia can be caused or exacerbated by aspirin. For the management of dyspepsia or related symptoms please follow the flow diagram (see figure 2) and corresponding notes. Please also refer to NICE guidelines.[77]

Figure 2. Management of Dyspepsia



These notes refer to the points on the management of dyspepsia flow diagram (figure 2).

a. The trial treatment should be withheld whenever there are moderate or severe symptoms of dyspepsia (CTCAE v4 grade ≥ 2) or whenever symptoms are unacceptable to the participant. The clinical decision to withhold trial treatment CRF should be completed.
b. All participants with any dyspepsia should undergo *H.pylori* testing. Where there is an indication for upper gastrointestinal endoscopy, *H.pylori* testing should be performed at the

same time. Otherwise *H.pylori* testing can be performed by a carbon-13 urea breath test or stool antigen test (a two week PPI wash out period is required before breath or stool antigen testing) or can be performed by laboratory based serology where the test has been locally validated[77]. Any participant found to be *H.pylori* positive should undergo eradication therapy according to local protocols.

c. Where indicated upper gastrointestinal endoscopy should be performed. For indications please refer to the UK NICE guidelines for the management of dyspepsia.[77]
d. A proton pump inhibitor (PPI) should be initiated or continued for the whole trial period where no contraindication exists. The dose should be titrated up where symptoms persist to a maximum dose according to the British National Formulary (BNF).
e. Review medications for any other causes of dyspepsia (e.g. calcium antagonists or bisphosphonates) and offer life-style advice (see NICE dyspepsia guidelines[77]).
f. Where dyspepsia reoccurs or worsens (CTCAE v4 grade ≥ 2) after the trial treatment has restarted consider upper gastrointestinal endoscopy particularly if this has not already been performed and increase PPI therapy to a maximum dose according to the BNF.[78]
g. Those on the higher dose of trial treatment can have their dose reduced (dose level-1). MRC CTU will arrange for those taking 300mg aspirin or matched placebo to be reissued with 100mg aspirin or matched placebo. Those already taking 100mg aspirin or matched placebo will permanently discontinue the trial treatment.
h. Where the trial treatment is withheld for more than a total of 3 months the trial medication should be permanently discontinued. In the run-in period aspirin should be permanently discontinued if withheld for more than a total of 4 weeks.
i. Wherever the trial treatment has been permanently discontinued, follow-up in the trial should continue. Participants in the run-in phase will be asked for consent to allow passive follow-up data collection using medical records.

5.4.3.B Management of gastrointestinal bleeding

Aspirin induced bleeding can occur anywhere in the gastrointestinal tract but most commonly occurs from the stomach or oesophagus. Symptoms and signs of bleeding include dark tarry stools, vomiting of blood, either in the form of fresh blood or altered blood (often a coffee colour and consistency). Iron deficiency anaemia, both acute and chronic, is also an indication for investigation to exclude gastrointestinal bleeding. Where a participant develops gastrointestinal bleeding whilst taking the trial medication it should be permanently discontinued. Where gastrointestinal bleeding occurs in the trial run-in phase, aspirin should be permanently discontinued and participants should not be randomised. For guidance on the management of acute upper gastrointestinal bleeding please refer to the NICE guidelines for the management of gastrointestinal bleeding,(NICE CG141), available from: http://guidance.nice.org.uk/CG141/NICEGuidance/pdf/English.

5.4.3.C Management of other toxicities

Any of the following toxicities at any grade should result in the trial medication being immediately and permanently discontinued:

- gastrointestinal bleeding (see section 5.4.3.B)
- active gastrointestinal ulceration
- tinnitus or hearing loss
- macular degeneration
- intracranial bleeding
- hypersensitivity to aspirin
- other toxicities can be discussed with MRC CTU

For any other toxicity, the following principles are recommended:

- Trial treatment can be withheld (breaks of treatment up to 3 months are allowed) until the toxicity resolves and then consider reintroduction.
- In order to avoid unblinding, wherever possible, Investigators should investigate and manage symptoms under the assumption that the participant is receiving 300mg aspirin. However emergency unblinding is available (see section 5.6.1) if it will alter clinical management.
- If the participant is unable to tolerate treatment, contact MRC CTU to discuss indications and processes for a dose reduction. If a dose reduction is deemed appropriate and the participant is already receiving aspirin 100mg daily or matched placebo, this will result in discontinuation of trial treatment. If receiving aspirin 300mg daily or matched placebo, the lower dose or matched placebo will be supplied.
- Where the trial treatment is withheld for more than a total of 3 months the trial medication should be permanently discontinued. In the run-in period aspirin should be permanently discontinued if withheld for more than a total of 4 weeks.
- Wherever the trial treatment has been permanently discontinued follow-up in the trial should continue. Participants who discontinue during the run-in phase will be asked for consent to allow passive follow-up data collection using medical records.

Where uncontrolled hypertension develops during the course of the trial, the trial treatment should be withheld until the participants blood pressure is controlled.

5.4.4 PREGNANCY

Regular use of aspirin may adversely affect a pregnancy and/or foetal development. Regular aspirin use whilst breast feeding can also cause complications in the neonate/infant and should be avoided.[78] Therefore, participants joining Add-Aspirin should not be pregnant or breast feeding at registration and be advised against becoming pregnant during the trial treatment period. If a participant becomes pregnant during the trial, the trial treatment should be stopped and the pregnancy CRF and SAE form should be completed. This should also be discussed directly with the Trial Manager. Follow-up within the trial should continue.

5.5 OVERDOSE OF TRIAL TREATMENT

Should an aspirin overdose be suspected, the trial treatment should be withheld and local guidance and pathways should be followed. For additional guidance please contact the National Poisons Information Service (www.toxbase.org). MRC CTU should be informed about all aspirin overdoses and the appropriate adverse event reporting should be followed, see section 7. In the event of overdose, emergency unblinding is available (see section 5.6.1).

5.6 UNBLINDING

Randomisation codes are held within the MRC CTU randomisation system. Since blinding is critical to the integrity of the study, unblinding a participant's trial treatment during the trial is strongly discouraged unless it is a medical emergency and will alter clinical management.

5.6.1 EMERGENCY UNBLINDING

Unblinding should generally only be considered in the event of a medical emergency (for example, an emergency operation is required or an overdose has been taken) where knowledge of the participant's treatment allocation would change clinical management. Where unblinding is being considered during working hours (Mon - Fri, 09:00 - 17:00 UK time), the case should first be

discussed with the MRC CTU by contacting the Add-Aspirin Trial Managers who will contact one of the Trial Physicians. Out of hours, the Investigator (or assigned deputy) should have determined that the information is necessary, i.e. that it will alter the participant's immediate management. When the emergency is clearly not related to the investigational product, the problem may be appropriately managed by assuming that the participant is receiving the highest possible dose of active product (300mg aspirin), without the need for unblinding. Where it is deemed necessary, unblinding can only be performed by the Investigator or an authorised delegate via an access-controlled system available through the trial website (**www.addaspirintrial.org**).

Unblinding for any purpose other than a medical emergency is generally not allowed, but individual cases should be discussed with the MRC CTU if it is believed to be necessary for the medical care of the participant. Wherever possible, unblinding should be avoided to protect the integrity of the Add-Aspirin trial.

For any treatment code unblinding, the reason for the decision to unblind and the parties involved must be documented in the participant's medical record and on the Unblinding CRF. Treatment identification information should be kept confidential and should be disseminated only to those individuals that must be informed for medical management of the participant. Wherever possible, the trial teams involved in the day-to-day running of the projects (MRC CTU, TMH, CRO) will remain blinded.

5.6.2 UNBLINDING FOR SAFETY REPORTING

MRC CTU staff who are not involved in the day-to-day running of the trial will be responsible for unblinding possible suspected unexpected serious adverse reactions (SUSARs) and notable events for notification to the regulatory authorities.

5.7 PROTOCOL TREATMENT DISCONTINUATION

In giving consent to participate in the trial, participants are giving consent to have trial treatment, trial follow-up and data collection. However, an individual participant may stop treatment early for any of the following reasons:

- Unacceptable toxicity or adverse event
- Intercurrent illness that prevents further treatment
- Any change in the participant's condition that justifies the discontinuation of treatment in the Investigator's opinion. This might include prescription of aspirin or another medication that the Investigator feels could not safely be given alongside the trial treatment.
- Inadequate compliance with the protocol treatment in the judgement of the Investigator (compliance should be discussed and documented at each follow-up visit as indicated in the assessment schedule)
- Pregnancy
- Early cessation of trial treatment by the participant

As participation in the trial is entirely voluntary, a participant may choose to discontinue the trial treatment at any time without giving any reason, and without their medical care or legal rights being affected. Although the participant is not required to give a reason for discontinuing their trial treatment, any reasons given will be documented on the early cessation of trial treatment CRF..

Participants should remain in the trial for the purpose of follow-up and data analysis unless they additionally wish to withdraw their consent for this. If a participant wishes to withdraw from trial follow-up, refer to section 6.8.

5.8 TREATMENT FOLLOWING DISEASE RECURRENCE/PROGRESSION

When disease recurrence has occurred, participants should normally continue to take their allocated trial treatment. Where the Investigator feels that this is not appropriate (for example, if the participant will be receiving another treatment that cannot safely be given alongside the trial medication), this should be managed and documented as with any other treatment discontinuation (see section 5.7) and the participant should continue to be followed up in the trial wherever possible. See also section 5.11.4 for guidance on managing participants that require non-trial medication. A temporary discontinuation of trial medication could be considered. Unblinding should not normally be required. It is preferable to assume that the participant is taking an active product (300mg aspirin) and discontinue trial medication (either temporarily or permanently) if necessary. Individual cases can be discussed with the MRC CTU.

Note that disease recurrence is an important outcome event in all four tumour site-specific cohorts and should be assessed according to protocol definitions (see section 10.2) and documented on the appropriate CRF(s).

5.9 ACCOUNTABILITY & UNUSED DRUG

Pharmacies will be provided with trial-specific drug accountability procedures in the Add-Aspirin pharmacy pack.

5.10 ADHERENCE

A high rate of adherence to treatment is required and Investigators are responsible for ensuring that participants understand this. Prior to registration, Investigators and any other trial staff involved in the consent process should ensure that participants fully understand the trial treatment and the importance of adherence, and that over-the-counter aspirin or products containing aspirin must not be taken. This should be re-iterated at face-to-face (or telephone) follow-up visits at the specified time points and adherence should be positively encouraged. Patient-reported adherence should be recorded on follow-up CRFs. Please refer to section 6.2 for guidance on assessing adherence during the run-in period

5.11 NON-TRIAL TREATMENT

5.11.1 MEDICATIONS PERMITTED

All non-contraindicated medications that the responsible clinician feels are appropriate, for example, PPI, paracetamol and remedies for cough and colds, are allowed in the trial. However, the potential for interaction with aspirin of all medicines should be checked against the information provided by the BNF (www.bnf.org) or local equivalent. Information on concomitant medication that has potential anti-cancer activity will be collected at each follow-up visit and call.

5.11.2 MEDICATIONS NOT PERMITTED

Medications not permitted include anti-coagulant and anti-platelet medication, aspirin (including over the counter preparations) and others including methotrexate. See appendix IV for a list.
Regular NSAID use is not permitted. NSAIDs should be avoided wherever possible but short-term intermittent/occasional NSAID use is allowed (maximum of 2 consecutive weeks of regular use). Long-term systemic corticosteroids are not permitted but short-term intermittent use is allowed (maximum of two consecutive weeks). See appendix IV for further details. Participants should be counselled about over the counter aspirin and NSAID use prior to registration and this should be reinforced at follow-up visits.

5.11.3 MEDICATIONS TO BE USED WITH CAUTION

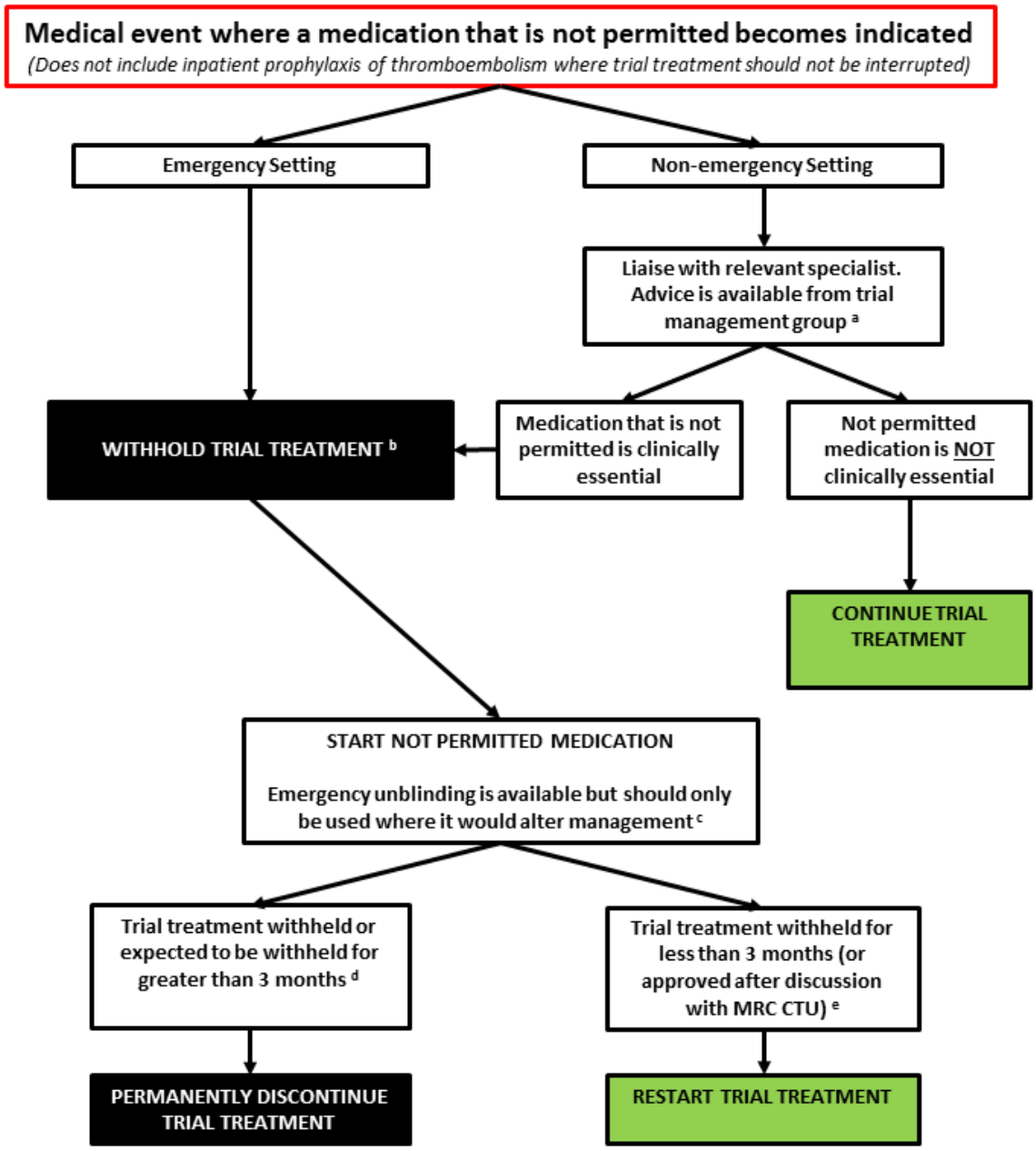
Aspirin has the potential to interact with the following medications: selective serotonin reuptake inhibitors (SSRIs), Iloprost, kaolin, metoclopramide, phenytoin, probenecid, spironolactone, sulfinpyraxone, thiopental, valproate, venlafaxine and zafirlukast. See the BNF for further details and a full list of interactions.

5.11.4 MANAGEMENT WHERE A MEDICATION THAT IS NOT PERMITTED BECOMES INDICATED DURING THE TRIAL

We would not expect patients who require a medication that is not permitted in the trial (see appendix IV) to be registered for Add-Aspirin because this should have been identified previously. However there may be participants who develop a medical condition during the trial where a medication that is not permitted becomes clinically indicated. Examples include but are not limited to: anti-coagulation for the treatment of pulmonary embolism, deep vein thrombosis or atrial fibrillation and anti-platelet therapy for the management of cardiovascular events.

For management where a medication that is not permitted becomes indicated see the flow diagram in (figure 3 – page 60) and corresponding notes.

Figure 3. Management where a medication that is not permitted becomes indicated



These notes refer to the points on the flow diagram in figure 3.

a. Where a medication that is not permitted is thought to be clinically essential the investigator should liaise with the relevant specialist (e.g. a cardiologist) to make this decision. Advice on individual cases will also be available from the Add-Aspirin trial management group which includes cardiovascular experts.
b. In an emergency situation the trial treatment should be immediately withheld and the non-permitted medication started. This should be reviewed with the relevant specialist advice at the first available opportunity. Unblinding should be avoided if possible.
c. Emergency unblinding is available but should only be performed where knowledge of the trial treatment would alter immediate clinical management (see section 5.6.1).

d. Where the trial treatment is withheld or expected to be withheld for more than 3 months the trial treatment should be permanently discontinued. The participant should continue to be followed up in the trial. Participants in the run-in phase will be asked for consent to allow passive follow-up data collection using medical records.
e. The trial treatment can be restarted when all medications that are not permitted have been discontinued and it has been withheld for less than 3 months (if greater than 3 months, individual cases can be discussed with MRC CTU).

Prescribing aspirin for its analgesic, anti-pyrexic or anti-inflammatory actions to provide symptomatic relief (e.g. headache, toothache, migraine, neuralgia, sore throat and dysmenorrhoea) should be avoided and alternative medications (e.g. paracetamol) should be considered.

MRC CTU should be informed of any event where a medication that is not permitted becomes indicated. The appropriate SAE form and/or CRF should be completed within 24 hours of the Investigator becoming aware of the event (see section 7).

6 ASSESSMENTS & FOLLOW-UP

6.1 TRIAL ASSESSMENT SCHEDULE

The frequency of follow-up visits and assessments are detailed in the Trial Assessment Schedule (see page xi - xiv). As far as possible, trial follow-up visits and assessments have been aligned with standard practice.

6.2 PROCEDURES FOR ASSESSING SUITABILITY FOR RANDOMISATION FOLLOWING THE RUN-IN PERIOD

Assessments at the end of the run-in period will focus on treatment adherenece and toxicity in order to determine the participant's suitability for randomisation into the trial. Participants will be provided with a diary card to complete during the run-in treatment period. They will be asked to bring this, along with their used blister packs, to their subsequent visit and these will be used to assess adherence. Toxicity will be assessed and documented using CTCAE v4 as for all other follow-up visits. Other assessments at this time include a blood test, blood pressure and an update on usage of concomitant medications, all of which will be assessed as described in section 6.4 for other follow-up visits.

Participants will be suitable for randomisation if they have taken at least 80% of their run-in treatment (6 or 7 tablets per week) and have not experienced any aspirin-related severe toxicity (defined as ≥grade 3 CTCAE v4), nor any grade of gastrointestinal bleeding, active gastrointestinal ulceration, tinnitus, macular degeneration, intracranial bleeding or hypersensitivity to aspirin. The Investigator is responsible for the final decision as to whether participants are suitable to be randomised but the Trial Management Group will be available for discussion via the Trial Manager if there are concerns or uncertainties.

The run-in period can be extended where the Investigator decides there is a valid reason for inadequate adherence (e.g. unforeseen social circumstances), or the cause of inadequate adherence is temporary (e.g. reversible dyspepsia, see section 5.4.3.A). Where offered, the run-in period would normally be extended by 4 or 8 weeks after which adherence and toxicity would be reassessed in the same way. All extensions to the run-in period must be pre-approved by MRC CTU via the Trial Managers and only one extension is permitted per participant.

6.3 PROCEDURES FOR ASSESSING EFFICACY

Clinical outcome events, as defined in the Statistical Analysis Plan, will be reported on case report forms (CRFs) to be completed by the Investigator or Research Nurse at each follow-up assessment. Disease recurrence and progression will be assessed at follow-up clinic visits by means of imaging, clinical examination and tumour markers (e.g. carcinoembryonic antigen (CEA), prostate-specific antigen (PSA)) in accordance with routine investigations for that tumour site (see Trial Assessment Schedule).

Following disease recurrence/progression, participants should normally continue to take their trial medication (see section 5.8 for guidance on treatment following relapse/progression). Providing they are willing, they should continue to be followed up in the trial, regardless of whether they are still receiving trial medication Follow-up should adhere as far as possible to the planned assessment

schedule, but some variation is acceptable where this differs from local protocols for follow-up after relapse.

6.4 PROCEDURES FOR ASSESSING SAFETY, ADHERENCE AND OTHER TRIAL EVENTS

Toxicity and adverse events will be assessed and documented at each follow-up assessment using CTCAE v4 in addition to expedited reporting of SAEs (see section 7).

Participant self-reported adherence, as well as concomitant medications, will be documented on CRFs at each follow-up assessment. Blood tests will be performed at some visits, including a fasting sample at the time of registration. Blood pressure and weight will also be checked.

In order to facilitate an assessment of the overall impact of aspirin on health outcomes, the occurrence of key events/diagnoses (including vascular events, thrombotic events, diabetes and associated complications, dementia, and age-related macular degeneration) will be documented on CRFs.

Note that the above assessments can be conducted via telephone follow-up where no clinic visit is planned providing that all the required information can be obtained (with the exception of blood pressure and weight which can be omitted if the participant is not due to attend clinic). A subset of participants may also be asked if they would agree to participate in a sub-study directly reporting trial-related outcomes through a web-based system.

6.5 CHARLSON COMORBIDITY INDEX

The presence of comorbidities will be assessed using the Charlson Comorbidity Index.[79] This 22-item questionnaire will be performed once at trial registration. It illustrates the extent to which a patient suffers from common comorbidities. Patients are assessed for the presence of various co-morbidities, with points allocated to each comorbidity if the condition is present. Points range from 1 to 6, with greater weighting given to items that are considered more serious. The final score is a weighted co-morbidity score and is calculated as the total number of points allocated for the patient.

6.6 VULNERABLE ELDERS SURVEY (VES-13)

Functional capacity will be assessed using the VES-13.[80] This will be performed for participants that are 65 years old or over at trial registration,both at registration and 5 years after randomisation. This 13-item, self-reported questionnaire can be administered in person or via the telephone, and assesses vulnerability across four domains: age, health in comparison to others, physical function and functional disability. The survey has a maximum final score of 10, with an upper limit put on the number of points awarded for each domain. The VES-13 survey will allow an investigation of the overall health benefits of aspirin in older people. This is also being assessed in the ASPREE study.

6.7 MONTREAL COGNITIVE ASSESSMENT (MOCA)

The hypothesis that aspirin protects against cognitive decline will be assessed using the MoCA. This 8-item questionnaire tests cognitive functioning across five domains: attention, language, abstraction, memory recall and orientation. The MoCA takes approximately ten minutes to complete

and will be administered in all Add-Aspirin participants at registration, then again at one and five years after randomisation.

6.8 EARLY STOPPING OF FOLLOW-UP

If trial treatment is discontinued, for whatever reason, this should be documented on the relevant CRF and the participant should continue to be followed up, providing they are willing. That is, they should be encouraged not to withdraw from the trial completely; if they do not wish any further follow-up data to be collected, however, their decision must be respected and the participant will be withdrawn from the trial completely. The MRC CTU should be informed of this by email, and receipt will be confirmed. Participants stopping follow-up early have a negative impact on trial data, so this should be avoided where possible.

Consent for future use of stored samples already collected can be withdrawn when leaving the trial early (and this should be indicated when notifying the CTU of the withdrawal), but this should be discussed with the participant and avoided where possible.

If participants change their minds about stopping trial follow-up at any time, please contact MRC CTU to discuss re-enrolment.

Participants who stop trial follow-up early will not be replaced, but the sample size allows for a degree of loss to follow-up.

Participants in the UK will be followed up in the long-term through NHS electronic data records available, which will include flagging with the NHS Information Centre and other national registries and healthcare databases (see section 9.3.1). Consent for this aspect of follow-up should be indicated on the consent form at the time of registration and the MRC CTU should be informed in writing if the participant later wishes to withdraw consent, but this should be discussed with the participant and avoided where possible.

In both countries, every effort should be made by Investigators to follow-up participants on a long-term basis. For participants who stop follow-up early, data collected up to the time of withdrawal from follow-up will be kept and included in the analysis unless the participant explicitly withdraws consent for this.

6.9 PARTICIPANT TRANSFERS

If a participant moves from the area, every effort should be made for them to be seen at another participating trial centre, and this should be discussed with the MRC CTU at the earliest opportunity. A copy of the participant's CRFs should be provided to the new centre and the participant will need to sign a new consent form. Once this has been done, the new centre will take over responsibility for the participant within the trial; until this has been done, responsibility for the participant lies with the original centre.

6.10 TRIAL CLOSURE

The trial will be considered closed 6 years after the last participant is randomised. However, further observational follow-up of participants enrolled in the trial will continue.

7 SAFETY REPORTING

The principles of ICH GCP require that both Investigators and sponsors follow specific procedures when notifying and reporting adverse events or reactions in clinical trials. These procedures are described in sections 7.1- 7.4.

7.1 DEFINITIONS

The definitions of the EU Directive 2001/20/EC Article 2 based on the principles of ICH GCP apply to this trial protocol. These definitions are given in table 5.

Table 5: Definitions

TABLE	DEFINITION
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial participant to whom a medicinal product has been administered including occurrences that are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product (IMP) related to any dose administered.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in the Summary of Product Characteristics (SPC) for that product.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)	Respectively any adverse event, adverse reaction or unexpected adverse reaction that: ▪ Results in death ▪ Is life-threatening* ▪ Requires hospitalisation or prolongation of existing hospitalisation** ▪ Results in persistent or significant disability or incapacity ▪ Consists of a congenital anomaly or birth defect ▪ Is another important medical condition***

*The term life-threatening in the definition of a serious event refers to an event in which the participant is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, for example, a silent myocardial infarction.
**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition (including elective procedures that have not worsened) do not constitute an SAE.
*** Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. The following should also be considered serious: important AEs or ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above; for example, a secondary malignancy, an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not result in hospitalisation or development of drug dependency.

7.1.1 MEDICINAL PRODUCTS

An IMP is defined as the tested investigational medicinal product and the comparators used in the study. (EU guidance ENTR/CT 3, April 2006 revision). In Add-Aspirin, aspirin and the placebos are IMP, including the aspirin used during the run-in period.

Adverse reactions include any untoward or unintended response to drugs. Reactions to an IMP should be reported appropriately.

7.1.2 CLARIFICATIONS AND EXCEPTIONS

Adverse Events include:

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event or condition
- A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration
- Continuous persistent disease or a symptom present at baseline that worsens following administration of the study treatment

7.1.3 EXEMPTED ADVERSE EVENTS

Adverse Events do not include:

- Recurrence of primary cancer – this should be reported on the appropriate CRF
- Death due to primary cancer – this should be reported on the appropriate CRF
- Diagnosis of another cancer – this should be reported on the appropriate CRF
- Medical or surgical procedures; the condition that leads to the procedure is the adverse event
- Pre-existing disease or a condition present that was diagnosed before trial treatment that does not worsen
- Hospitalisations where no untoward or unintended response has occurred, e.g. elective cosmetic surgery, social admissions
- Grade 1 events and grade 2 events where there are no clinical symptoms

7.2 OTHER NOTABLE EVENTS

7.2.1 PREGNANCY

Pregnancy occurring during participation in the Add-Aspirin trial should be reported on an SAE form and sent to the MRC CTU within 24 hours of the Investigator being aware of the pregnancy. Treatment should usually be discontinued (see section 5.4.4).

Any pregnancy that occurs in a trial subject will be followed to termination or to term and the appropriate CRF completed. Follow-up of a child born to a trial subject who received treatment in the trial during pregnancy will be as per standard clinical care. The clinical team responsible will be asked to inform the MRC CTU if there is any suspicion of any adverse effect of the trial medication.

7.3 INVESTIGATOR RESPONSIBILITIES

All non-serious AEs and ARs, whether expected or not, should be recorded in the participant's medical notes and reported in the toxicity section of the relevant follow-up form and sent to the MRC CTU within one month. The MRC CTU should be notified of all SAEs and SARs within 24 hours of the Investigator becoming aware of the event.

7.3.1 INVESTIGATOR ASSESSMENT

7.3.1.A Seriousness

When an AE or AR occurs, the Investigator responsible for the care of the participant must first assess whether or not the event is serious using the definition given in table 5. If the event is serious **and not only related to disease progression or another event exempted from expedited reporting**, then an SAE form must be completed and the MRC CTU notified with 24 hours.

7.3.1.B Severity or grading of adverse events

The severity of all AEs and/or ARs (serious and non-serious) in this trial should be graded using the toxicity gradings in appendix V (CTCAE v4).

7.3.1.C Causality

The Investigator must assess the causality of all serious events or reactions in relation to the trial therapy using the definitions in table 6. There are five categories: unrelated, unlikely, possible, probable, and definitely related. If the causality assessment is unrelated or unlikely to be related, the event is classified as an SAE. If the causality is assessed as possible, probable or definitely related, then the event is classified as an SAR.

Table 6: Assigning Type of SAE Through Causality

RELATIONSHIP	DESCRIPTION	SAE TYPE
Unrelated	There is no evidence of any causal relationship.	Unrelated SAE
Unlikely	There is little evidence to suggest that there is a causal relationship (for example, the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (for example, the participant's clinical condition, other concomitant treatment).	Unrelated SAE
Possible	There is some evidence to suggest a causal relationship (for example, because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (for example, the participant's clinical condition, other concomitant treatments).	SAR
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	SAR
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR

If an SAE is considered to be related to trial treatment and drug may need to be stopped or the dose modified, refer to section 5.4.

7.3.1.D Expectedness

An unexpected adverse reaction is one not previously reported in the current SPC or one that is more frequent or more severe than previously reported. The definition of an unexpected adverse

reaction (UAR) is given in table 5. Please see appendix V for a list of expected toxicities associated with aspirin. If a SAR is assessed as being unexpected, it becomes a SUSAR. If there is at least a possible involvement of the trial treatment, the Investigator should make an initial assessment of the expectedness of the event. The sponsor will have the final responsibility for determination of expectedness (for reporting purposes), and this decision will be made on the basis of the above definition and the information provided by the Investigator.

7.3.1.E Notification

The MRC CTU should be notified of all SAEs within 24 hours of the Investigator becoming aware of the event.

Investigators should notify the MRC CTU of all SAEs occurring from the time of registration until 30 days after the last protocol treatment administration. SARs and SUSARs must be notified to the MRC CTU until trial closure.

7.3.2 NOTIFICATION PROCEDURE

1. The SAE form must be completed by the Investigator (a clinician named on the Signature List and Delegation of Responsibilities Log who is responsible for the participant's care), with due care being paid to the grading, causality and expectedness of the event as outlined above. In the absence of the responsible Investigator, the form should be completed and signed by a member of the centre trial team and faxed or emailed as appropriate. The responsible Investigator should subsequently check the SAE form, make changes as appropriate, sign and then re-fax to the MRC CTU as soon as possible. The initial report must be followed by detailed, written reports as appropriate.

   The minimum criteria required for reporting an SAE are the participant's trial number and date of birth, name of Investigator reporting and why the event is considered serious.

2. The SAE form must be sent by fax or scanned and emailed to the MRC CTU. Receipt will be confirmed.
   Fax: +44 (0)20 7670 4818
   Email: mrcctu.add-aspirin@ucl.ac.uk

3. Follow-up: participants must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilised. Follow-up should continue after completion of protocol treatment if necessary. A further SAE form(s), indicated as 'Follow-up' should be completed and faxed or scanned and emailed as an encrypted file to the MRC CTU as information becomes available. Extra, annotated information and/or copies of test results may be provided separately. The participant must be identified by trial number, date of birth and initials only. The participant's name should not be used on any correspondence and should be deleted from any test results.

4. Staff should follow their institution's procedure for local notification requirements.

SAE REPORTING
Within 24 hours of becoming aware of an SAE, please send a
completed SAE form to the MRC CTU by fax or email (scanned and encrypted copy):
Fax: +44 (0)20 7670 4818
Email: mrcctu.add-aspirin@ucl.ac.uk

7.4 MRC CTU RESPONSIBILITIES

The Chief Investigator, one of the tumour site-specific Lead Investigators or a medically-qualified delegate will review all SAE reports received. The causality assessment given by the local Investigator at the hospital cannot be overruled; in the case of disagreement, both opinions will be provided in any subsequent reports.

The MRC CTU is undertaking the duties of trial sponsor and is responsible for the reporting of SUSARs and other SARs to the regulatory authorities in the UK and the research ethics committees, as appropriate. Fatal and life-threatening SUSARs must be reported to the Competent Authorities within 7 days after the MRC CTU becoming aware of the event; other SUSARs must be reported within 15 days. Expedited reporting and report submission in India will be delegated to a CRO.

The MRC CTU will submit Annual Safety Reports in the required format to Competent Authorities (Regulatory Authority and Ethics Committee). Submission of Annual Safety Reports to Indian authorities will be delegated to the CRO.

The MRC CTU will also keep all Investigators informed of any safety issues that arise during the course of the trial.

Bayer Pharmaceuticals AG will also be notified of all SUSARs, SARs and other notable events. MRC CTU will also provide Bayer Pharmaceuticals with a copy of the Development Safety Update Report (DSUR).

8 QUALITY ASSURANCE & CONTROL

8.1 RISK ASSESSMENT

The Quality Assurance (QA) and Quality Control (QC) considerations have been based on a formal risk assessment, which acknowledges the risks associated with the conduct of the trial and how to address them with QA and QC processes. QA includes all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the principles of GCP and applicable regulatory requirements. QC includes the operational techniques and activities done within the QA system to verify that the requirements for quality of the trial-related activities are fulfilled. This risk assessment has been reviewed by the MRC CTU Research Governance Committee (RGC).

8.2 CENTRAL MONITORING AT MRC CTU

MRC CTU staff will review CRFs for errors and missing data points and send query reports to centres or raise queries on the database at regular intervals for data clarification.

Other essential trial issues, events and outputs will be detailed in the monitoring plan, data management plan and safety management plan which will be based on the trial-specific risk assessment.

8.3 ON-SITE MONITORING

The frequency, type and intensity of routine on-site monitoring and the requirements for triggered monitoring will be detailed in a monitoring plan. This plan will also detail the procedures for review and sign-off.

8.3.1 DIRECT ACCESS TO PARTICIPANT RECORDS

Participating investigators should agree to allow trial related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data and documents as required. Participant's consent must be obtained for this.

8.3.2 CONFIDENTIALITY

It is intended to follow the principles of the UK Data Protection Act regardless of the countries where the trial is being conducted.

9 ANCILLARY STUDIES

9.1 THROMBOXANE B_2 STUDIES

Serum thromboxane B_2 (TXB2), a product of platelet aggregation, is known to be a indicator of cyclooxygenase activity and will be measured to study adherence to aspirin at the end of the run-in period in a subgroup of participants. Serum samples will be collected from 500 participants (at selected UK centres) and analysed centrally using a validated assay for measurement of TXB2. Results will be compared with participant-reported adherence data, and will be extrapolated to allow estimation of the extent and potential impact of non-adherence overall in the trial. The study may also indicate differences in the effects of aspirin on platelet function in cancer patients compared with previous studies of healthy individuals.

Subject to funding, we also plan to initiate a substudy to measure urinary excretion of 11-dehydro-thromboxane B_2 in a subgroup of participants at a number of time points throughout the trial. This will both contribute to the analysis of adherence, as well as facilitating investigation of TXB2 as a potential biomarker of aspirin efficacy.

Urinary excretion of 11-dehydro-thromboxane B_2 (TXB2) (a major enzymatic metabolite of thromboxane A2/thromboxane B2) provides an indication of baseline platelet activation, and it's use has been demonstrated in the evaluation of the role of platelet activation in atherothrombosis.[81] Persistent platelet activation as reflected by enhanced excretion of thromboxane metabolites, has been reported in association with major cardiovascular risk factors that accelerate atherogenesis suggesting that platelet activation links a number of diverse metabolic and hemodynamic abnormalities. Platelets also trigger autocrine and paracrine processes that result in phenotypic changes in stromal cells that may contribute to the development and spread of cancer.[82] Platelets are thought to affect the development and spread of metastases by facilitating the adhesion of cancer cells to circulating leukocytes and endothelial cells and permitting adhesion to the endothelium and transmigration.[18] Since low-dose aspirin (75-100mg daily) is thought to have negligible direct biological effects apart from on the anucleate platelet, one of the primary hypotheses regarding mechanisms of action is that aspirin may achieve anti-cancer effects by inhibiting platelet function. In the cardiovascular setting, urinary concentrations of 11-dehydro TXB2 have been shown to predict risk of cardiovascular events in patients receiving aspirin, thus providing a potential biomarker for identifying individuals who are unlikely to benefit from the cardiovascular effects of aspirin.[83]

9.2 SAMPLE COLLECTION FOR FUTURE TRANSLATIONAL RESEARCH

We have applied for funding to support an Add-Aspirin bio-bank which will provide a unique collection of samples with prospective and systematically collected randomised data on aspirin use, cancer outcomes and other potential healthcare benefits related to aspirin. It is intended that the bio-bank will be used for a number of translational studies that will be developed and introduced during the trial, subject to securing the appropriate funding. Studies will be reviewed by the TSC and the ethics committee prior to initiation. The tissue collection will also be made accessible to other research groups via application to an Access Committee.

The bio-bank will be jointly hosted by three Institutions: Tayside Tissue Bank and the Wales Cancer Bank in the UK, and the Advanced Centre for Treatment, Research and Education in Cancer (ACTREC) in India.

9.2.1 TIMING AND PRACTICALITIES OF SAMPLE COLLECTION

All participants will be asked to donate formalin fixed paraffin embedded (FFPE) tumour sample and a blood sample at baseline. Participants will be asked to provide consent for sample collection at the time of registration but may choose to opt-out of this aspect of the trial. Participants are still eligible for the trial if they choose not to participate in any of the sample collections.

Approaching participants about sample donation at the time of registration will allow blood samples to be collected prior to any aspirin administration including from participants who are subsequently found to be unable to tolerate aspirin during the run-in period. Sub-studies into non-tolerance of aspirin could provide important information which would be applicable across all indications for aspirin use.

The majority of FFPE samples will be from primary surgical tumour specimens, however participants who have undergone radical chemoradiotherapy (gastro-oesophageal cancer participants), radical radiotherapy (prostate cancer participants) or neoadjuvant chemotherapy for breast cancer (where there is minimal residual tumour at excision) will have specimens collected from diagnostic biopsy samples. FFPE samples will be returned from the bio-bank to their centre of origin upon request.

In the UK, one 10ml whole blood sample will be collected prior to any aspirin administration and will be posted in a Royal Mail Safe Box to one of the two UK repositories. Arrangements for the sample collection in India will be confirmed.

9.2.2 PIK3CA MUTATIONS

The potential importance of PIK3CA mutations to predict response to aspirin, particularly in colorectal cancer, has been identified.[24, 26] Subject to funding, samples from participants in this cohort will be used to test for the PIK3CA mutation during the run-in period and this will be incorporated as a stratification factor at randomisation. Plans for analyses of the impact of the PIK3CA mutation are outlined in section 10.3.1, with a corresponding power assessment in section 10.4.6.A. The effect of PIK3CA mutation status on aspirin efficacy will also be considered in the other tumour site-specific cohorts.

9.3 TRIAL METHODOLOGY STUDIES

9.3.1 USE OF ROUTINELY-COLLECTED HEALTHCARE DATA AND PARTICIPANT-REPORTED DATA FOR TRIAL FOLLOW-UP

Additional outcome data for UK trial participants will be obtained from routinely-collected healthcare databases provided by the National Cancer Intelligence Network (NCIN) and other relevant organisations. This will augment the trial dataset and provide long-term data after the end of active trial follow-up. Data collected will include dates and causes of death (from national registries); serious aspirin-related toxicity and cardiovascular morbidity (from hospital episode data); details of cancer recurrence (from cancer registries); and potentially aspirin prescription data (from GP records). Participants will be asked to provide consent for this aspect of the study during registration and, for the purpose of data linkage, trial Investigators will be required to record participant NHS numbers, date of birth and sex on case report forms.

A period of overlap between active trial follow-up and passive follow-up data collection is planned to allow an assessment of the completeness and suitability of these routinely-collected healthcare datasets for investigating the long-term outcomes of interest in Add-Aspirin. In addition, some participants may be asked to directly provide an update on their health status through a web-based

programme so that we can compare health outcomes derived from all three potential sources. This embedded methodological sub-study will take place during the early years of follow-up and will compare data on trial events identified through medical records, as well as participant-reported events, with Investigator-reported event data collected within the trial. The results will have implications both for follow-up within the ongoing trials, as well as for future trials.

9.3.2 ASSESSING DIFFERENT APPROACHES TO TRIAL CONDUCT

The size and scope of the trial provides the opportunity to evaluate different approaches to trial conduct. In particular, strategies to facilitate the conduct of the trial at participating centres will be evaluated.

10 STATISTICAL CONSIDERATIONS

10.1 METHOD OF RANDOMISATION

Randomisation will be performed separately within each tumour-specific cohort and will use minimisation algorithms based on key prognostic factors (dependent on tumour site) and incorporating a random element. In order to further reduce determinability, minimisation factors are not listed here. Randomisation will be performed on a double-blind basis, so that neither the treating Investigator nor the participant will be aware of whether the participant has been allocated to aspirin or a placebo.

Following successful completion of the run-in period, the majority of participants (those under 75 years old) will be randomised 1:1:1 to 100mg aspirin, 300mg aspirin or placebo (matching either 100mg aspirin or 300mg aspirin).

Elderly participants (≥75 years) will undergo a double-blind 2:1 randomisation to 100mg aspirin or placebo (matching 100mg aspirin). The 2:1 ratio ensures that they will have the same chance of receiving an active treatment as other participants.

10.2 OUTCOME MEASURES

The primary aims of the trial are to assess whether aspirin can prevent recurrence and prolong survival in individuals who have had radical treatment for cancer. This will be achieved by means of a combined cohort analysis on overall survival including all four cohorts. Allied to this, cohort-specific analyses will allow investigation of the specific effects of aspirin on each tumour type.

Overall survival is a key outcome of interest in Add-Aspirin that will allow an assessment of the overall health benefits of adjuvant aspirin in patients with early stage cancer. However, with the exception of the gastro-oesophageal cohort, using overall survival as the primary outcome in the tumour-specific comparisons would lead to unfeasibly large sample sizes and results emerging many years later in comparison with alternative outcome measures such as disease- or recurrence-free survival. This is because we can anticipate a smaller treatment effect on overall survival, and relatively good cancer-related outcomes in these patient groups, with many patients dying from causes other than cancer in all but the gastro-oesophageal cohort. The additional power afforded by the combined cohort analysis, due to its larger sample size and longer follow-up, will allow an assessment of overall survival across all cohorts.

10.2.1 PRIMARY OUTCOME MEASURES

For the combined cohort analysis, the primary outcome measure will be time to death from any cause. The cohort specific primary outcome measures are also all time-to-event variables and are defined in table 7. Details of outcome assessments are given in section 6.

Table 7: Primary outcome measures

COHORT	PRIMARY OUTCOME MEASURE*
Cohorts combined	**Overall survival (OS)**
Breast cancer	**Invasive disease-free survival (IDFS)**
Colorectal cancer	**Disease-free survival (DFS)**
Gastro-oesophageal cancer	**Overall survival**
Prostate cancer	**Biochemical recurrence-free survival (bRFS)**

*These will be defined in the statistical analysis plan.

10.2.2 SECONDARY OUTCOME MEASURES

There are a number of secondary outcome measures that are common to all cohorts, as well as some cohort-specific outcomes, as defined in the table below. Secondary outcomes will be important for providing a comprehensive assessment of the potential health benefits and risks of the treatment. Details of outcome assessment are given in section 6. Major secondary outcome measures for each cohort are defined below.

Table 8: Secondary outcome measures

COHORT	SECONDARY OUTCOME MEASURE
All cohorts	**Overall survival** Time from randomisation to death from any cause (note that this is the primary outcome for the gastro-oesophageal cohort)
	Adherence Based on participant-reported compliance with taking tablets. During the run-in period, adherence will additionally be assessed on the basis of returned blister packs and diary cards. There will also be a translational sub-study to assess adherence based on thromboxane B_2 levels measured in serum samples (see section 9.1).
	Toxicity Based on CTCAE v4
	Serious haemorrhage CTCAE (v4) grade 3 or greater
	Serious vascular events Non-fatal myocardial infarction, non-fatal stroke or vascular deaths (using the definition applied by the Antithrombotics Trialists' collaboration)[84]
	Thrombotic events Diagnosis of venous thromboembolism
	Diabetes and associated complications Diagnosis of diabetes or associated complications (including retinopathy, impaired renal function)
	Second malignancies Diagnosis of a new primary cancer
	Age-related macular degeneration (AMD) Diagnosis of AMD
	Cognitive assessment Using the Montreal Cognitive Assessment (MoCA)
	Dementia Diagnosis of dementia (of any type), reported by sub-type

COHORT	SECONDARY OUTCOME MEASURE
	Comorbidities Using the Charlson Index
	Obesity Using the Body Mass Index (BMI)
	Functional capacity Using the VES-13 questionnaire
Breast	**Breast cancer-specific survival** Time from randomisation to breast cancer death
	Bone metastases-free survival Time from randomisation to development of bone metastasis or death from any cause
	IDFS-DCIS Defined as for IDFS except that ductal carcinoma in situ (DCIS) (ipsilateral or contralateral) is additionally included as an event[85]
Colorectal	**Colorectal cancer-specific survival** Time from randomisation to colorectal cancer death
Gastro-oesophageal	**Disease-free survival** Time from randomisation to disease recurrence or death from any cause
Prostate	**Prostate cancer-specific survival (PCSS)** Time from randomisation to prostate cancer death
	Time to initiation of salvage treatment Time from randomisation to initiation of salvage treatment
	Bone metastases-free survival Time from randomisation to development of bone metastasis or death from any cause

10.3 ANALYSIS METHODS

Preliminary data[86] and some of the postulated mechanisms of action for aspirin means that there is a strong possibility that any effect of aspirin may only emerge after a period of time. In such 'delayed effect' situations, the assumption of proportional hazards, under which the logrank test is uniformly most powerful, is called into question. However, it is not possible to predict reliably when a delayed effect may appear. Consequently for each cohort we have done the following:

1) We have calculated the sample size for the cohort based on a desire to attain a given power using the logrank test and assuming proportional hazards for a given targeted hazard ratio, in the usual way
2) We have also calculated the power of the logrank test with this sample size assuming that survival curves do not separate for the first 2 years (i.e. a delayed effect) and that the mean hazard ratio from the start of the study to the time of analysis is equal to the targeted hazard ratio

During the course of recruitment to the four cohorts we shall formally review any evidence external to the trial which may give information on the likely impact of aspirin on the survival distribution for one or more cohorts. If good evidence emerges that aspirin will have little or no effect for the first 3 years (or more) for any of the cohorts we shall consider changing the primary test from the logrank test to a joint test which considers both the hazard ratio and the time-dependent bahaviour of the hazard ratio and is likely to have much more power in this situation[87]. To ensure that this involves

only evidence external to the trial the decision to change the test will be made by the Trial Steering Committee (TSC), who do not have access to the accumulating results from the four cohorts, rather than the Independent Data Monitoring Committee (IDMC).

For the power calculations (and analysis) of the cohorts combined, we have used the joint test, stratified by cohort. This is because we anticipate that aspirin will have a late effect on overall survival, with curves separating at 3 years (and possibly beyond this). In this situation the joint test is likely to be considerably more powerful than the logrank alone.

Sample size and power calculations for the individual cohorts and combined analysis are given in section 10.4.

10.3.1 SUBGROUP ANALYSES BY PIK3CA MUTATION STATUS

Published data from recent studies[24, 26] in colorectal cancer suggest that the effect of aspirin on DFS may be greater in patients who have the PIK3CA mutation than in those who do not, and in fact any effect of aspirin may be limited to this group alone. Subject to funding, this hypothesis will be formally tested in the colorectal cohort through additional comparisons which will follow the same general principles (and occur at the same time) as the primary analyses.

In order to limit the impact on the overall type I error rate of carrying out multiple significance tests, the comparisons to be performed (and their significance level) will depend on the outcome of the primary analysis as follows:

1) In the event that the primary analysis of DFS demonstrates a statistically significant effect of aspirin two subsequent analyses will be carried out; in particular, patients with the PIK3CA mutation and those without will be analysed as separate subgroups. These analyses will be conducted at an overall 2-sided significance level of 5%. The significance level for each of the two tests will be determined by Holm's method[88], but will be either 2.5% or 5%. By performing this closed procedure and conditioning on obtaining a significant result in the primary analysis, we ensure that no adjustment is needed to preserve the type I error rate for the primary analysis.
2) In the event that the primary analysis does not demonstrate a statistically significant effect of aspirin, a single subsequent analysis of only those patients with the PIK3CA mutation will be performed. A 1% 2-sided significance level will be used in order to limit the impact on the overall type I error rate for this and the primary analysis. Given that the primary analysis will be conducted using a 5% significance level, the overall type I error rate associated with performing both tests is at most 6%.

Sample size and power calculations for the subgroup analyses outlined above are given in section 10.4.6.A for the colorectal cohort.

Comparisons of aspirin vs. placebo both in patients with and without the PIK3CA mutation will form part of the planned secondary analyses in the other cohorts and shall be structured in a similar way to the colorectal cohort.

10.4 SAMPLE SIZE

In calculating an appropriate sample size for the trial, each cohort is considered separately in order to 1) account for the differences in disease behaviour and recruitment between tumour sites

observed in previous studies and 2) ensure that the individual cohort-specific comparisons are adequately powered.

In the combined analysis, as well as for the cohort-specific analyses, the primary comparison will be aspirin vs. placebo (with the two aspirin arms combined). Each individual cohort is sized under proportional hazards to ensure 90% power to detect the targeted effects of aspirin on the primary outcome measures with the exception of the gastro-oesophageal cohort, which has 80% power. The target effect sizes are of a similar magnitude across the four cohorts and represent realistic effect sizes, similar to those seen for a range of adjuvant therapies across cohorts. They may be smaller than target effect sizes in some adjuvant trials where potential benefits are balanced against higher costs and greater toxicity of the experimental therapy.

The analysis of the cohorts combined is planned for approximately 15 years after the first recruitment into the trial, with the intention of assessing the long-term anti-cancer effects of aspirin. For each cohort-specific comparison, analyses are planned for 5-6 years after recruitment of the last participant to that cohort, but the exact timing will be based on the number of outcome events that have been observed. The sample sizes needed to observe the required number of events are estimated based on anticipated recruitment rates (informed by recruitment rates in previous similar trials and a feasibility survey of participating Investigators), including allowance for slower accrual during the earlier stages of the study, and a small percentage of participants having incomplete follow-up data on the outcome of interest. The total sample size across four cohorts combined will be approximately 9,920 participants.

10.4.1 BREAST COHORT

In the breast cohort, based on data from recent trials of adjuvant chemotherapy in similar breast cancer cohorts (specifically TACT,[89] BIG 02-98[90] and GEICAM[91]), as well as results from the recent Indian study of pre-operative progesterone[92], and additionally considering that a gradual improvement has been observed over time in outcomes for these patients, 5-year IDFS in the control group is expected to be approximately 80%. The number of patients for this cohort is designed to have 90% power at a 5% 2-sided significance level to demonstrate a 4% absolute improvement in this rate at 5 years (corresponding to hazard ratio, HR=0.78).

Assuming proportional hazards, this will require 717 IDFS events to be observed, with 275 events in the control group. Assuming that the cohort takes $3^1/_2$ years to recruit, with the analysis taking place 6 years after the last randomisation, and that complete primary outcome data will not be obtainable for approximately 10% of participants by the time of analysis, the anticipated sample size needed to observe this number of events is 3100.

If an effect of aspirin were not observed for the first two years, it is estimated that the power achieved by the logrank test at the time of analysis would be approximately 83% with the proposed sample size. This calculation assumes a hazard ratio of 1 (no effect) over the first two years followed by a hazard ratio of 0.71 thereafter, which yields a mean hazard ratio of approximately 0.78 (the targeted hazard ratio for this cohort) at the time of the primary analysis of the cohort.

10.4.2 COLORECTAL COHORT

In the colorectal cohort, based on data from recent trials of adjuvant chemotherapy regimens in similar cohorts of colorectal cancer patients (specifically MOSAIC[93] and QUASAR[94]), and also considering that the Add-Aspirin cohort will be more mixed (including patients who haven't had chemotherapy and older patients), 5-year DFS in the control group is expected to be 70%. The

cohort is designed to have 90% power at a 5% 2-sided significance level to demonstrate an absolute 5% improvement in this rate at 5 years (corresponding to HR=0.80).

Assuming proportional hazards, this will require 899 DFS events to be observed, with 336 events in the control group. Assuming that the cohort takes $3^1/_2$ years to recruit, with the analysis taking place 6 years after the last randomisation, and that complete primary outcome data will not be obtainable for approximately 10% of participants by the time of analysis, the anticipated sample size needed to observe this number of events is 2600.

If an effect of aspirin were not observed for the first two years, it is estimated that the power achieved by the logrank test at the time of analysis would be approximately 85% with the proposed sample size. This calculation assumes a hazard ratio of 1 (no effect) over the first two years followed by a hazard ratio of 0.72 thereafter, which yields an estimated mean hazard ratio of 0.8 (the targeted hazard ratio for this cohort) at the time of the primary analysis of the cohort.

10.4.3 GASTRO-OESOPHAGEAL COHORT

Estimation of the control arm survival rate for the gastro-oesophageal cohort, considers data from patients who underwent a complete resection in RTOG8911[95] and MRC OE02[96] (trials of pre-operative chemotherapy in oesophageal cancer), a US trial of post-operative chemoradiation in gastric and junctional tumours[97] and the MAGIC trial[98] (of peri-operative chemotherapy in gastric and lower oesophageal cancer), and additionally takes into account a gradual improvement in outcomes over time in this patient group, observed in recent years, as reflected in data from the UK National Oesophago-Gastric Cancer Audit 2012[99]. On this basis, 5-year survival in the control group is expected to be 45%. The cohort is designed to have 80% power at a 5% 2-sided significance level to demonstrate a 6% absolute improvement in this rate at 5 years (corresponding to HR=0.84).

Assuming proportional hazards, this will require 1120 deaths to be observed, with 402 deaths in the control group. Assuming that the cohort takes 6 years to recruit, with the analysis taking place 5 years after the last randomisation, and that complete primary outcome data will not be obtainable for approximately 10% of participants by the time of analysis, the anticipated sample size needed to observe this number of events is 2100.

If an effect of aspirin were not observed for the first two years, it is estimated that the power achieved by the logrank test at the time of analysis would be approximately 77% with the proposed sample size. This calculation assumes a hazard ratio of 1 (no effect) over the first two years followed by a hazard ratio of 0.65 thereafter, which yields an estimated mean hazard ratio of 0.84 (the targeted hazard ratio for this cohort) at the time of the primary analysis of the cohort.

Whilst the above target effect size is reasonably conservative based on the effects observed by Rothwell et al,[86] given that the therapy is low-cost and easy to administer, with low rates of toxicity, it is acknowledged that a smaller benefit in terms of cancer outcomes may still be clinically relevant, but powering the study to detect this would lead to an unfeasibly large sample size. Nevertheless, 2100 participants will provide approximately 70% power to detect a 5% difference in disease-free survival at 3 years (corresponding to HR=0.86), assuming that 3-year disease-free survival in the control group is 50%.

10.4.4 PROSTATE COHORT

The prostate cohort is powered separately for those who have undergone radical prostatectomy prior to entry and for those who have had radical radiotherapy. The cohort is designed to have 90% power in each of these groups to demonstrate an 8% absolute improvement in 5-year bRFS based on

a 5% 2-sided significance level. It is assumed that both groups will take 5 years to recruit, with the primary analysis taking place 5 years after the last randomisation, and that complete primary outcome data will not be obtainable for approximately 15% of participants at the time of analysis (largely due to deaths from causes other than prostate cancer).

In the radical prostatectomy group, the 5-year bRFS in the control arm is expected to be 75% and an 8% improvement corresponds to HR=0.65[100]. Assuming proportional hazards, a total of 230 bRFS events, with 96 events in the control group, will be required to detect this effect with 90% power and the anticipated sample size is 920.

In the radical radiotherapy group, based on data on intermediate and high-risk patients in RT01 (a recent trial of escalated-dose conformal radiotherapy),[101] 5-year bRFS in the control arm is expected to be 65% and an 8% improvement corresponds to HR=0.73. Assuming proportional hazards, a total of 443 bRFS events, with 173 events in the control group, will be required to detect this effect with 90% power and the anticipated sample size is 1200.

Thus, the prostate cohort will recruit approximately 2120 participants in total (prostatectomy and radiotherapy groups combined), with 5-year bRFS in the two control arms combined expected to be approximately 69%. With this sample size, the trial will have approximately 90% power at a 5% 2-sided significance level to detect an absolute improvement in 5-year bRFS of 6% (corresponding to HR=0.78) in this combined cohort (with assumptions about timelines and data completeness as in the separate calculations).

If an effect of aspirin were not observed for the first two years, it is estimated that the power achieved by the logrank test at the time of analysis would be approximately 87% with the proposed sample size. This calculation assumes a hazard ratio of 1 (no effect) over the first two years followed by a hazard ratio of 0.68 thereafter, which yields an estimated mean hazard ratio of 0.78 (the targeted hazard ratio for this cohort) at the time of the primary analysis of the cohort.

10.4.5 Analysis of Cohorts Combined

The power of the combined analysis of overall survival at 15 years (after the first randomisation) is evaluated here based on the total sample size of 9,920 patients calculated in the previous section. Hazard ratios that are detectable with 90% power are presented, assuming that an effect of aspirin only emerges after a period of time. Because it is not possible to reliably predict when an effect of aspirin may emerge, hazard ratios are presented for a range of delayed effects. Calculations are performed based on the joint test, stratified by cohort (see section 10.3).

Estimates of overall survival in the individual cohorts are taken from recent trials in comparable populations as follows:

- In the breast cohort, based on data from recent trials of adjuvant chemotherapy in similar breast cancer cohorts (TACT,[89] BIG 02-98[90] and GEICAM[91]) 5-year OS in the control group is expected to be 90%.
- In the colorectal cohort data from the MOSAIC[93] and QUASAR[94] trials suggest that 5-year OS in the control group is likely to be approximately 80%.
- In the gastro-oesophageal cohort 5-year control group OS is expected to be 45%, as discussed in section 10.4.3.
- In the prostate cohort, data from the EORTC[100] trial in patients receiving radical prostatectomy, along with the results of the RT01[101] trial in patients undergoing radical radiotherapy suggest that 5-year OS will be approximately 90% in the control group.

Incorporating these estimated survival rates, the table below summarises the estimated hazard ratios that will be detectable with 90% power at the 5% significance level. The effects that it is possible to detect here are relatively small in comparison with the cohort-specific analyses because the joint test has more power than the logrank test in delayed effect situations, with greater savings in power for effects that take longer to emerge.

Table 9: Combined cohort analysis: minimum detectable hazard ratios at a 5% significance level with 90% power

TIMING OF EFFECT OF ASPIRIN	HAZARD RATIO
Emerges after 3 years	0.92
Emerges after 4 years	0.92
Emerges after 5 years	0.93

As a consequence of the event rates in the four cohorts it is anticipated that the gastro-oesophageal cohort will contribute approximately half of the events in this analysis. Thus to assess the consistency of the overall result, a separate analysis will be done without the gastro-oesophageal cohort.

10.4.6 FURTHER ANALYSES

10.4.6.A Subgroup analyses defined by the PIK3CA mutation in the colorectal cohort

Data from recent trials[24, 26] indicate that the incidence of the PIK3CA mutation in patients with colorectal cancer is approximately 15%. Therefore, it is anticipated that approximately 390 of the planned 2600 patients in the Add-Aspirin colorectal cohort will have the mutation.

Depending on the outcome of the primary analysis, the significance level used in the analysis of patients with the PIK3CA mutation will be either 1%, 2.5% or 5% (see section 10.3.1). At these significance levels and with 390 patients this analysis will have 90% power to detect hazard ratios of 0.48, 0.51 or 0.54 respectively.

Under Holm's method, the significance level used in the analysis of patients without the PIK3CA mutation may be either 2.5% or 5%. With an anticipated 2210 such patients, this analysis will have 90% power to detect hazard ratios of 0.76 or 0.78 respectively.

10.4.6.B Power for assessing the effects of aspirin on incidence of serious vascular events in the prostate cohort

Serious vascular events will be an important secondary outcome in the prostate cohort since a significant proportion of men will have received adjuvant androgen deprivation therapy and, given the age of these men and concerns regarding cardiovascular risk associated with this therapy, there may be additional benefits to incorporating aspirin into treatment algorithms for prostate cancer. Based on rates of serious vascular events in the general population of men aged 65-84 years (the expected age of the prostate cohort) as reported in the Oxford Vascular Study,[102] as well as data on rates of cardiovascular disease in men with prostate cancer from a large population-based study in Sweden,[103] it is anticipated that approximately 10% of the prostate control group will have experienced a serious vascular event by the end of the 5-year treatment period in Add-Aspirin. Given the planned sample size of 2120, the study will have more than 80% power to detect an absolute improvement of just under 3%, corresponding to HR=0.7, with aspirin based on a 5% 1-sided significance level. This is a realistic target benefit compared to improvements observed with aspirin

in previous studies. In a meta-analysis by the Antithrombotic Trialists' Collaboration a 2.5% reduction in serious vascular events was observed for high-risk individuals on aspirin (from 13.2% to 10.7%, HR approximately 0.8). The Add-Aspirin prostate cohort will have 70% power to detect an absolute improvement of a similar magnitude (2.4%, corresponding to HR=0.75) with a 5% 1-sided significance level.

10.4.6.C Power for assessing the effects of aspirin on prostate cancer-specific survival (PCSS)

In a later, long-term analysis, planned for approximately 15 years after the first randomisation, PCSS will be a key outcome. Given the planned sample size of 2120 (radiotherapy and prostatectomy groups combined) and assuming that 10-year PCSS is 90% in the control arm, and that complete primary outcome data will not be obtainable for approximately 20% of participants at the time of analysis (largely due to deaths from causes other than prostate cancer), this analysis is expected to have just over 90% power to detect a 4% improvement (to 94%, corresponding to HR=0.59), with a 2-sided 5% significance level.

Considering the radiotherapy cohort separately (n=1200), and assuming that 10-year PCSS in the control arm of this group will be 88%, the long-term analysis is expected to have more than 80% power to detect a 5% improvement (to 93% at 10 years, HR=0.57) with all other assumptions as previously. Considering the prostatectomy group (n=920), and taking the control arm 10-year PCSS to be 92%, the long-term analysis will have more than 70% power to detect a 4% improvement (to 96% at 10 years, HR=0.49) with all other assumptions as previously.

In a study of approximately 6000 men in the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database who had undergone radical prostatectomy or radical radiotherapy for localised adenocarcinoma of the prostate, Choe et al observed improvements in 10-year prostate cancer-specific mortality of 3% (from 6% to 3%) and 15% (from 19% to 4%) for the intermediate- and high-risk groups respectively with anticoagulant use.[62] Therefore, the above target differences seem reasonable.

10.5 INTERIM MONITORING AND ANALYSES

Whilst the trial is ongoing data will be analysed on a regular basis for review by the IDMC. These analyses will remain confidential and available to the IDMC only. An IDMC Charter will be drawn up that describes the membership of the IDMC, relationships with other committees, terms of reference, decision-making processes, and the timing and frequency of interim analyses (see section 14.3). It is expected that the committee will meet to review the data at least annually up to the time of the primary analyses. Permission may be sought from the IDMC to release data relating to completed sub-studies, the run-in period and methodological sub-studies of trial conduct or other issues where release of such data would not jeopardise the overall integrity of the trial.

There will be no formal stopping rules for the trials; however a formal feasibility assessment (described below) is planned early during the course of the study. Any decision to discontinue recruitment at any time, in all participants, in specific cohorts or in selected subgroups, will take into consideration all relevant information from both the trial and external sources and will only be made if the result is likely to convince a broad range of people including participants in the trial and the general clinical community. For example, a p-value of the order of 0.001 on the primary outcome measure, together with supporting data on other outcome measures, might be needed for the IDMC to recommend ceasing recruitment to any specific cohort or for reporting results before the planned number of events have been reached. In coming to a view the IDMC should consider that aspirin is

being used as 'maintenance treatment' in this trial, and presentation of results earlier than anticipated may prevent the ability to assess longer term effects of adjuvant aspirin, because of the potential for use of aspirin in the control arm of the cohorts.

Any decision to cease recruitment or report early would be made by the TSC on the basis of recommendations from the IDMC (see section 14).

10.6 FEASIBILITY PHASE

The study incorporates a formal assessment of feasibility planned for two years from the time when, for each tumour site, there are at least 30 open centres in the UK that have recruited a participant. At this time, as in their regular reviews, the IDMC will review all trial data, but with a particular focus on recruitment, treatment tolerability and adherence. The committee will be asked to review recruitment rates relative to pre-specified targets, as well as giving particular consideration to data on serious adverse events, tolerability and adherence, with the aim of confirming that there are no safety concerns, and that the trial remains viable with the planned recruitment targets and timelines. Use of the run-in period will also be reviewed at this time. The IDMC will make recommendations to the TSC and TMG regarding continuation of the trials, and may choose to release some of the data to them if appropriate.

Note that this formal feasibility assessment will not necesarily be the first review by the IDMC (since they are expected to meet at least annually from the start of recruitment). Since safety data available at an earlier time is likely to be informative, this will be a key component of earlier IDMC reviews, and the committee will make recommendations on the basis of the accumulating data in the normal way.

10.7 TIMING OF PRIMARY AND OTHER PLANNED ANALYSES

Separate primary analyses will be performed for each cohort and will take place approximately 5-6 years after recruitment of the last participant for that cohort (between 9 and 11 years after recruitment of the first participant), with the exact timing based on the observed numbers of events.

Following the four cohort specific analyses, combined analyses across all four cohorts are planned for approximately 15 years after recruitment of the first participant. The longer follow-up associated with this analysis will enable any long-term benefits of aspirin to be realised. Furthermore, the pooled cohort will provide additional power to address the dose question and to assess toxicity outcome measures that are relevant to all cohorts such as serious haemorrhage rates, serious vascular events and second malignancy rates. Data collected during the trial period will be supplemented by long-term data from medical records (see section 9.3.1) in order to provide 15-year follow-up for this analysis.

10.8 ANALYSIS PLAN (BRIEF)

The analyses will be described in detail in a full Statistical Analysis Plan developed by the trial Statistician(s) and finalised prior to the primary analyses.

10.8.1 PRIMARY ANALYSES

Primary analyses will compare cancer outcomes for participants allocated to aspirin (100mg and 300mg arms combined) and participants allocated to placebo, regardless of the treatment received (i.e. intention-to-treat). The primary analyses will include both those participants <75 years who underwent the full randomisation and those ≥75 years who underwent randomisation between 100mg aspirin or placebo only, but the dose effects of aspirin will be investigated only on those randomised between the two doses.

Primary comparisons will be made with adjustment for prognostic factors as outlined in the Statistical Analysis Plan. The impact of this adjustment will be considered in secondary analyses.

10.8.2 ASPIRIN DOSE COMPARISON

If an overall effect of aspirin vs. placebo is observed in the primary treatment comparison for one or more cohorts, a further analysis will be performed to investigate differences in efficacy according to aspirin dose. This analysis will be performed only in the cohorts that show a positive result for aspirin vs. placebo and will be stratified by cohort. By making these analyses conditional on a benefit of aspirin being observed in the primary analysis, the likelihood of a false-positive result is reduced. The rationale for combining the data across cohorts is to maximise power, as we anticipate that any difference between doses of aspirin will be smaller than the difference between aspirin and placebo. Consideration of rates of serious toxicity (and particularly serious haemorrhage), as well as other secondary health outcomes, alongside the efficacy results will be particularly important in these analyses in order to provide an holistic assessment of the potential risks and benefits associated with different doses.

10.8.3 OTHER SECONDARY AND SUBGROUP ANALYSES OF TREATMENT EFFICACY

The analyses of primary outcomes will be repeated on a per protocol basis in order to assess the impact of non-adherence on the estimates of treatment effects. The cohorts to be included will be pre-specified in the analysis plan.

The effects of adjusting for prognostic factors will be considered in the treatment comparisons for the primary outcomes through unadjusted analyses. These comparisons will also be assessed in a small number of well-defined subgroups where there is thought to be the potential for differences in treatment efficacy. These will also be pre-specified in the analysis plan.

11 REGULATORY & ETHICAL ISSUES

11.1 COMPLIANCE

11.1.1 REGULATORY COMPLIANCE

The trial complies with the principles of the Declaration of Helsinki 2008.

It will also be conducted in compliance with the approved protocol, the principles of GCP as laid down by the Commission Directive 2005/28/EC with the implementation in national legislation in the UK by Statutory Instrument 2004/1031 (The Medicines for Human Use [Clinical Trials] Regulations 2004) and subsequent amendments, the UK Data Protection Act (DPA number: Z5886415), the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF), and with regulatory legislation in each participating country.

11.1.2 CENTRE COMPLIANCE

All centres will comply with the above, and non-UK centres will additionally comply with any applicable national regulations. An agreement will be in place between the centre and the MRC CTU, setting out respective roles and responsibilities.

The centre will inform the MRC CTU as soon as they are aware of a possible serious breach of compliance, so that the CTU can report this breach, if necessary, within 7 days as per the UK regulatory requirements. For the purposes of this regulation, a 'serious breach' is one that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects in the trial, or
- the scientific value of the trial.

The Investigator or a delegate should document and explain any deviation from the approved protocol. This should be communicated to the trial team at the MRC CTU.

11.1.3 DATA COLLECTION AND RETENTION

CRFs, clinical notes and administrative documentation should be kept in a secure location (for example, locked filing cabinets in a room with restricted access) and held for 15 years after the end of the trial. During this period, all data should be accessible to the competent or equivalent authorities, the Sponsor and other relevant parties with suitable notice. The data may be subject to an audit by the competent authorities.

11.2 ETHICAL CONDUCT OF THE STUDY

11.2.1 ETHICAL CONSIDERATIONS

Participation in a randomised controlled trial means that the participant and clinician are not able to choose all aspects of treatment but do choose for the participant to be randomised. Participants will receive different treatments and toxicities are different by arm; this will be explained to participants.

Additional hospital visits and tests (over and above routine care) may be required for the trial though follow-up will be aligned with standard care wherever possible. There will not be any reimbursement if costs are incurred for patients in the UK. Travel and incidental expenses will be reimbursed for participants in India if additional hospital visits are made that are not routine.

Placebo arms have been included in the Add-Aspirin trial to make the treatments seem as similar as possible from the participant's perspective. Importantly, even closer similarity between the trial arms is achieved by preventing investigators knowing which treatment the participant is receiving (double-blind).

A run-in period has been included to identify those individuals who may experience unacceptable toxicities related to aspirin use and those who are unlikely to be able to adhere to the protocol treatment schedule. For those who experience severe toxicity related to aspirin use and/or those who are unable to adhere to the protocol treatment schedule, active participation in the trial will end at this time and they will not go on to be randomised. However, they will be asked if they wish to give consent to allow passive follow-up data collection using medical records.

Participants in the UK will be followed-up in the long-term through routinely-collected healthcare databases provided by the NCIN and other organisations. This may include aspirin prescriptions, morbidity data and mortality data. Participants will be asked to consent to this separately and can still participate in the trial if they do not give their consent to this aspect of the trial.

Additional blood tests and other biological samples may be requested for future research. Participants will be asked to consent to this separately and can still participate in the trial if they do not give their consent to this aspect of the trial.

11.2.2 ETHICAL APPROVALS

Before initiation of the trial at each clinical centre, the protocol, all informed consent forms, and information materials to be given to prospective participants will be submitted to the appropriate ethics committees for approval. Any further amendments will be submitted and approved by these ethics committees.

The rights of the participant to refuse to participate in the trial without giving a reason must be respected. After the participant has entered into the trial, the Investigator must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the participant. The reason for doing so, however, should be recorded; the participant will remain within the trial for the purpose of follow-up and for data analysis. Similarly, the participant must remain free to change their mind at any time about the protocol treatment and trial follow-up without giving a reason and without prejudicing his/her further treatment.

11.3 COMPETENT AUTHORITY APPROVALS

This protocol will be submitted for review by the national competent or equivalent authority, as appropriate, in each country where the trial will be run.

This is a Clinical Trial of an IMP as defined by the EU Directive 2001/20/EC. Therefore, a CTA is required in the UK.

The EUdraCT number for the trial is 2013-004398-28.

The progress of the trial and safety issues will be reported to the competent authorities, regulatory agencies or equivalent in accordance with local requirements and practices in a timely manner.

Safety reports, including expedited reporting and SUSARS will be submitted to the competent authorities in accordance with each authority's requirements and in a timely manner.

11.4 OTHER APPROVALS

The protocol will be submitted by those delegated to do so to the relevant Research and Development (R&D) department of each participating centre or to other local departments for approval as required in each country. A copy of the local R&D approval (or other relevant approval as above), and of the PIS and consent form, on local headed paper should be forwarded to the MRC CTU for UK centres and the CRO for Indian centres before participants are entered.

12 INDEMNITY (UK)

The sponsor of the trial is the University College London (UCL) and the trial is coordinated by the MRC CTU at UCL, a department of UCL.

UCL holds insurance against claims from UK participants for injury caused by their participation in this clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in hospital, the hospital continues to have a duty of care to the participant of the clinical trial. UCL does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of UCL or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to UCL's Insurers, via the MRC CTU at UCL. Hospitals participating in Add-Aspirin must provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary should be provided upon request.

Insurance arrangements for India will be confirmed.

13 FINANCE

Add-Aspirin is funded by Cancer Research UK, the UK NIHR Health Technology Assessment Programme and MRC CTU.

Bayer Pharmaceuticals AG will provide the IMPs - aspirin 300mg, aspirin 100mg and matching placebos.

Add-Aspirin is included in the NCRN portfolio and support will be available for participating UK centres in the usual way.

14 OVERSIGHT & TRIAL COMMITTEES

There are a number of committees involved with the oversight of the trial. These committees are detailed below, and the relationship between them expressed in figure 3.

14.1 TRIAL MANAGEMENT GROUP (TMG)

The TMG comprises the Chief Investigator, other lead Investigators (clinical and non-clinical) and staff at the MRC CTU at UCL and Tata Memorial Hospital. The TMG will be responsible for the day-to-day running and management of the trial. Full details of the TMG functioning, including frequency of meetings, can be found in the TMG Charter. A list of TMG members can be found in appendix XII.

A sub-group of the TMG will be responsible for the development and day-to-day running of the sample collection and translational studies.

14.2 TRIAL STEERING COMMITTEE (TSC)

The TSC has membership from the TMG and representatives of the funder plus independent members, including an independent Chair. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chair. The ultimate decision for the continuation of the trial lies with the TSC. They will also act as an Access Committee for granting access to samples for external research groups. Further details of TSC functioning are presented in the TSC Charter.

14.3 INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

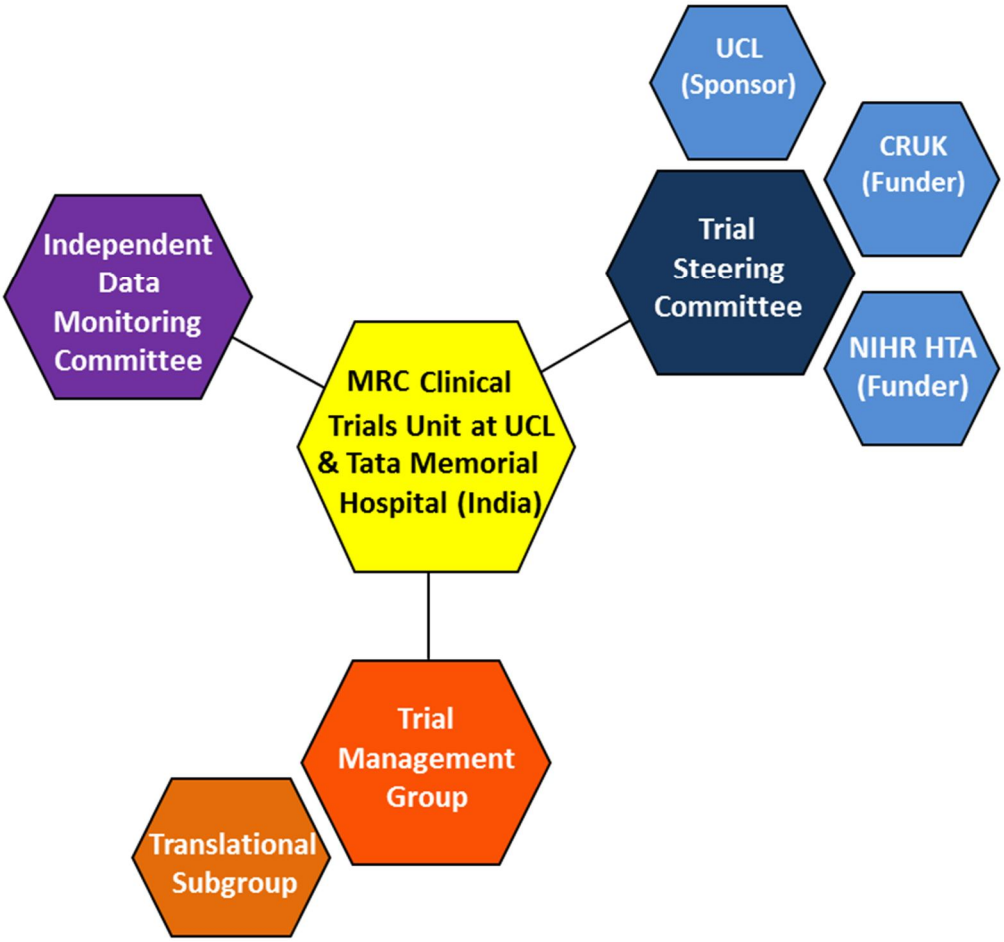
An IDMC will be formed. The IDMC will be the only group who sees the confidential, accumulating data for the trial. Reports to the IDMC will be produced by the MRC CTU. The frequency of IDMC meetings will be determined by the committee and detailed in the IDMC Charter. The IDMC will consider data using the Statistical Analysis Plan (see section 10.8) and will advise the TSC. The IDMC can recommend premature closure or reporting of the trial, or that recruitment to any research arm or tumour site-specific cohort be discontinued.

Further details of IDMC functioning and the procedures for interim analyses and monitoring are provided in the IDMC Charter.

14.4 ROLE OF STUDY SPONSOR

The sponsor of the trial is University College London, as employer of the staff coordinating the trial at the MRC CTU.

Figure 3. Diagram of relationships between trial committees



15 PUBLICATION AND DISSEMINATION OF RESULTS

15.1 PUBLICATION AND PRESENTATION OF TRIAL RESULTS

The results from different centres and participating countries will be analysed together and published as soon as possible in peer-reviewed journals, as well as being presented at national and/or international conferences. Individual groups and clinicians must not publish data concerning their participants that are directly relevant to questions posed by the study until the TMG has published its report. The TMG will form the basis of the Writing Committee and will advise on the nature of all publications.

There are expected to be a number of resulting publications and the authorship will vary for each. Individual authors are likely to include relevant members of the TMG and collaborators, as well as high-recruiting Investigators. All participating centres and corresponding PIs and co-PIs in the relevant cohort will be acknowledged in all relevant publications, along with members of the IDMC and TSC.

Results from the primary analyses of the four tumour site-specific studies will be available at different times, as will results from the sub-studies. In order not to jeopardise the integrity of the ongoing trials, careful consideration (in discussion with the IDMC and TSC, as appropriate) will be given to the data to be released from each analysis for presentation/publication. Similarly, if at any point it is felt to be justified and appropriate to release specific data from an interim analysis, this would require discussion and agreement from the IDMC, who would be asked to provide guidance regarding the data to be released and how widely they should be disseminated.

15.2 DISSEMINATION OF ONGOING PROGRESS AND RESULTS TO PARTICIPANTS AND THE PUBLIC

If participants have given permission, they will be contacted directly with the ongoing progress and results of the trial. Results will also be available to participants and the public on the Add-Aspirin website: addaspirintrial.org and through their clinician.

16 PROTOCOL AMENDMENTS

This is version 3.0 of the protocol.

16.1 PROTOCOL

16.1.1 AMENDMENTS MADE TO PROTOCOL VERSION 1.0 06-MAR-2014

1. Throughout – version and date updated to v2.0, 30-May-2014.
2. Throughout – minor typographical corrections and amendments for consistency and clarity.
3. Page iv – Trial contact details – telephone number updated.
4. Page v – Trial administration – addition of Clinical Project Manager's contact details.
5. Page vi – Correction of Lead Investigator's name.
6. Pages xi – xiv – Trial Assessment Schedule – TICS questionnaire replaced with Montreal Cognitive Assessment.
7. Section 3 – Selection of Participants – Addition of known lactose intolerance to exclusion criteria.
8. Section 6.6 – Montreal Cognitive Assessment replaces Telephone Interview of Cognitive Status.

16.1.2 AMENDMENTS MADE TO PROTOCOL VERSION 2.0 30-MAY-2014

1. Throughout – version and date updated to v3.0, 22-Sep-2014.
2. Throughout – minor typographical corrections and amendments for consistency and clarity.
3. Page ii – clarification that Bayer Pharmaceuticals AG are providing drug for the run-in period as well as randomised treatment.
4. Pages iv and v – trial contact details updated.
5. Front page and page vii – addition of REC number.
6. Page viii – clarification of registration process.
7. Page ix – clarification of information relating to sub-studies and addition of Tata Memorial Hospital as trial coordinator in India.
8. Pages xi – xiv – update of some assessment time points, addition of sample collection time points and addition of clarifications in footnotes.
9. Section 1.1 – update of cancer mortality data.
10. Section 2 – minor operational clarifications.
11. Section 3 – clarification of participant selection process.
12. Sections 3.1 – 3.8 – general clarifications, update of trial entry information, relocation of pregnancy/breast feeding criterion to exclusion criteria for clarity and relocation of footnotes to main body of text.
13. Section 3.10 – clarification of registration and randomisation procedures.
14. Section 4 – update of contact details.
15. Section 4.2 – clarification of timing of initiation of run-in period.
16. Section 5.1 – clarification regarding run-in treatment period.
17. Section 5.6.1 – clarification of unblinding procedures.
18. Section 5.7 – removal of disease recurrence as a reason to discontinue protocol treatment and clarification of treatment discontinuation procedures.
19. Section 5.8 – clarification of procedure for treatment following disease recurrence/progression.
20. Section 6.2 – addition of further information regarding assessing suitability for randomisation.
21. Sections 6.3 and 6.4 – clarifications on procedures for assessing efficacy, safety, adherence and other trial events.

22. Section 6.6 – clarification of timing of VES-13.
23. Section 6.8 – clarification of early stopping of follow-up procedure.
24. Section 7.3.2 – addition of requirement to send SAEs as encrypted files.
25. Section 9.1 – addition of information regarding the thromboxane B_2 studies.
26. Section 9.2 – addition of information regarding sample collection for future translational research.
27. Section 9.3.1 – clarification of use of routinely-collected healthcare data and participant-reported data for trial follow-up.
28. Throughout section 10 – minor clarifications.
29. Section 10.2.2 – Table 8 – addition of further information regarding assessment of adherence.
30. Section 11.2.1 – minor clarifications.
31. Section 12 – minor clarification regarding UK indemnity.
32. Section 14 – minor clarifications.

16.1.3 AMENDMENTS MADE TO PROTOCOL VERSION 3.0 22-SEP-2014

1. Section 7.3.1.D – clarification of sponsor's responsibility to determine expectedness of events.

16.2 APPENDICES

16.2.1 AMENDMENTS MADE TO APPENDICES VERSION 1.0 06-MAR-2014

1. Throughout – version and date updated to v2.0, 30-May-2014.
2. Participant Information Sheet, section 1 – addition of explanation that the placebo in Add-Aspirin contains lactose.
3. Participant Information Sheet, section 4 – addition of clarification that NSAIDs can be used occasionally for no more than two weeks at a time.
4. Participant Information Sheet, sections 4 and 5 – addition of explanation that participants will have their blood pressure checked at each trial visit.
5. Participant Information Sheet, section 6 – addition of disadvantage that participants will not be able to take NSAIDs on a regular basis.
6. Participant Information Sheet, section 8 – addition of full name of research ethics committee.
7. GP Letter – addition of explanation that NSAIDs can only be used occasionally for no more than two weeks at a time.
8. GP Letter – addition of explanation that participants will have their blood pressure checked at each trial visit and that any hypertension should be managed according to standard practice.
9. Trial Management Group – study updated to cohort.

16.2.2 AMENDMENTS MADE TO APPENDICES VERSION 2.0 30-MAY-2014

1. Throughout – version and date updated to v3.0, 22-Sep-2014.
2. Throughout – minor typographical corrections and amendments for consistency and clarity.
3. Front page – addition of REC number.
4. Participant Information Sheet – page 7 – update of sample collection information and clarification of stopping trial participation procedures.
5. Consent Form – page 10 – clarification that NHS records will be used even if participants are not randomised (but have given their consent for this).

6. Consent Form – page 11 – removal of urine sample permission and clarification regarding use of data for future research.
7. Consent Form – page 12 – update of consent form storage procedure.
8. GP Letter – page 13 – clarification of unblinding procedure.
9. Appendix IV – onwards – renumbering of appendices due to removal of biological sample collection table.
10. RADICALS and Add-Aspirin – page 22 – update of RADICALS diagram for clarity.
11. Trial Management Group and Collaborators – pages 23 – 24 – study changed to cohort and addition of translational research collaborators.

16.2.3 AMENDMENTS MADE TO APPENDICES VERSION 3.0 22-SEP-2014

1. Throughout – version and date updated to v4.0, 13-Nov-2014 for consistency with protocol.

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Appendices to the Add-Aspirin Protocol

Version: 4.0
Date: 11-Nov-2014

MRC CTU ID: AA01
ISRCTN #:
EudraCT #: 2013-004398-28
CTA #:
REC #: 14/SC/0171

CONTENTS

APPENDIX I – PARTICIPANT INFORMATION SHEET (UK)

(To be presented on local headed paper)

Version 4.0, 11-Nov-2014

Add-Aspirin Clinical Trial

We are inviting you to take part in a research study called the Add-Aspirin trial

- Before you decide whether to take part, it is important for you to understand why the research is being done and what it will involve.
- Please take time to read the following information carefully. Discuss it with friends and relatives if you wish. Take time to decide if you wish to take part.
- You are free to decide if you want to take part in this research study. If you choose not to take part, this will not affect the care you get from your own doctors in any way.
- You can decide to stop taking part in the study at any time without giving a reason.
- Ask your study doctor if anything is not clear or if you would like more information.
- Thank you for reading this information. If you decide to take part, we will ask you to sign a form to give your consent for each part of the study.

Important things that you need to know

- We are testing whether taking aspirin regularly after treatment for early stage cancer stops or delays the cancer coming back.
- We are testing different doses of aspirin. Some people will receive a dummy drug (placebo).
- Like all medicines, aspirin can have side-effects. The most common side-effects of aspirin are:
  - irritation of the stomach
  - indigestion
  - bleeding - this a serious side-effect of aspirin but it is uncommon.
- We expect that most people who take part in this study will need to visit the hospital approximately 12 times over 5 years depending on your cancer type. Whenever possible, this will be at the same time as your regular check-up visit.
- We will also ask if you would like to donate a small amount of blood, urine and tissue from your cancer for future research.

Contents

How to contact us

If you have any questions about this study, please talk to your doctor at
Hospital Department
Hospital
Address
Address
Tel: 01234 XXX XXX

1 Why are we doing this study?

This study is for people who have had or have started treatment for cancer of the breast, stomach, oesophagus (food pipe), prostate or bowel.

We are aiming to find out whether taking aspirin regularly after treatment for cancers that have not spread widely (early stage cancer), stops or delays the cancer coming back. This study will compare groups of people who take aspirin and those who take placebo tablets.

What is a placebo?

A placebo is a "dummy" tablet. It looks like an aspirin tablet but it doesn't contain any medicine. We are using a placebo in this study so that we can make as clear an assessment as possible about the effects of aspirin. Keeping everything exactly the same apart from what is contained in the tablet allows us to study just the effects of aspirin. The placebo used in Add-Aspirin contains lactose. People who are lactose intolerant will be excluded from taking part in the study.

What is the usual treatment?

Usually, people like you, who have had or have started treatment for early stage cancer, will come into hospital for regular check-ups once the treatment has finished. People who have had prostate cancer sometimes also take long-term hormone treatment. People who have had breast cancer sometimes also take long-term hormone treatment or Herceptin. This will continue if you take part in the study. People who have had stomach, oesophagus or bowel cancer don't usually take any other long-term treatments.

2 Why am I being asked to take part?

You are being invited to take part in the Add-Aspirin study because you have had or are having treatment for cancer of the breast, stomach, oesophagus, prostate or bowel. Although your doctors believe that they are able to successfully treat your cancer, some cancers unfortunately may come back. This study will find out whether or not taking aspirin regularly after treatment can stop or delay this happening.

3 What do I need to know about the medicines used in this study?

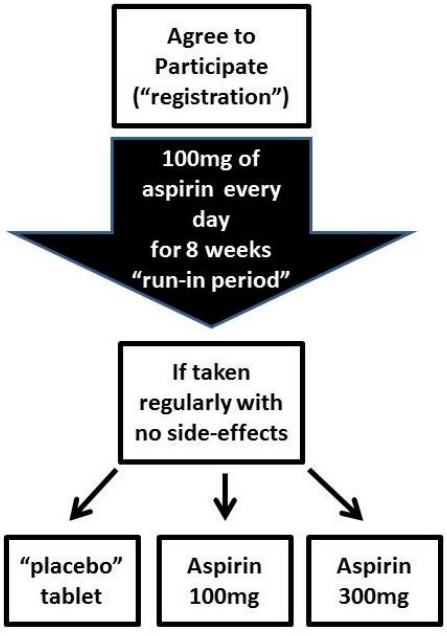
Aspirin is a common drug that is used as a painkiller and to prevent further heart attacks and strokes in some people. Some studies have suggested that people who regularly take aspirin may be less likely to be diagnosed with cancer than those who don't take aspirin. Also, in studies testing the beneficial effect of aspirin on heart disease, aspirin appeared to reduce the number of people who developed cancer, and if people did develop cancer, it appeared to be less likely to spread. So researchers believe that aspirin may stop cancer coming back in people who have had treatment for early stage cancer. But, importantly, there is not any reliable evidence yet since previous studies were not specifically designed to answer this question.

A clinical trial or study is the best way to test this. It will look at both the benefits and the side-effects of taking aspirin in a large group of people who have had cancer. The study will look at two different doses of aspirin. This is because little is known about how much aspirin may be needed to have an effect, if any, against cancer.

4 What will I need to do if I take part?

If you agree to take part in this study, you will have a blood test and be asked questions about your medical history to check your suitability to take part. In the study, you will be asked to take the study medicines for at least 5 years. We know that it can be difficult to take medicines every day over a long period so everyone will be asked to take 100mg of aspirin for about 8 weeks at the beginning of the study. This is called the "run-in" period and will help us to identify people who may have problems taking aspirin. If you find it difficult to take aspirin regularly, it may not be recommended that you continue. After 8 weeks, if taking aspirin every day hasn't caused you any problems, you will then be randomly allocated by computer to one of the three treatments:

1. 300mg of aspirin every day (one tablet per day) or
2. 100mg of aspirin every day (one tablet per day) or
3. A placebo tablet every day (one tablet per day).



If you are 75 years old or over, you will only be allocated to 100mg of aspirin or placebo. This is because you may be more likely to have side-effects from aspirin.

To make sure the results of this study are as reliable as possible, neither you, nor your doctor, will know which treatment you get. If your doctor needs to find out which treatment you are taking at some point during the study, they will be able to do so.
Whichever treatment you get, we will ask you to take one tablet a day for at least 5 years. It is very important that you take your tablet daily. It is usually easier to remember to do this if you take the tablet at the same time each day. If you forget to take a tablet or number of tablets do not take additional tablets to catch up, you should only take one tablet a day. Please let your study doctor or nurse know if you have missed any tablets next time you see them.

Who decides which treatment I will get?

A computer will choose which treatment you get by a process called 'randomisation'. This means you will have an equal chance of getting any one of the 3 treatments and ensures that the groups of people being compared in the study are as similar as possible to start with except for the treatment they take. This in turn ensures that any differences between these groups are only due to the treatments in the study.

Everyone joining this study will have a two out of three chance of getting aspirin.

Other medicines

It is **extremely** important that you do not take any other medication that contains aspirin regularly and you should not buy aspirin from a chemist or shop while taking part in the study. You should also not take drugs such as ibuprofen or Nurofen (non-steroidal anti-inflammatory drugs) on a regular basis but

they can be used occasionally where absolutely necessary for no more than two weeks at a time. If you need to use a painkiller for more than two weeks, please discuss an alternative with your doctor e.g. paracetamol. They will also give you more information about this if you decide to take part in this study.

Checks and tests

Before you start taking your study treatment, you will have a blood test. After the "run-in" period you will have a check-up and blood test to see if you have had any problems taking aspirin. You will then have a check-up, blood tests and other checks depending on your cancer type every three months until one year and then every six months after that.

If you were diagnosed with bowel cancer, you will have some CT scans. These would all be part of your normal care whether or not you participate in the study. The total dose of ionising radiation from these scans is approximately the same as 30 years of natural background radiation in the UK to which we are all exposed. The risk of a secondary cancer occurring from these scans is approximately 1 in 300, which is considerably less than our lifetime risk for developing cancer which is 1 in 3.

If you were diagnosed with breast cancer, you will have some mammograms. These would all be part of your normal care whether or not you participate in the study. The total dose of ionising radiation from these mammograms is approximately the same as three years of natural background radiation in the UK to which we are all exposed. The risk of a secondary cancer occurring from these mammograms is approximately 1 in 3000.

Some studies have suggested that aspirin may help protect against age-related changes in memory and thought processes (cognitive status). In order to find out more about this, we will ask you to complete a questionnaire at the beginning of the study, after one year and after five years.

You will have your blood pressure checked at each trial visit.

Your study nurse or doctor will be able to give you more information about these checks and tests.

5 What are the possible side-effects?

Aspirin is a common, frequently used drug and most people take it without experiencing any side-effects. We will ask you some questions about your medical history to check that aspirin is a suitable treatment for you but some people might experience some side-effects. Most side-effects are mild but, for a very small number of people, they can be serious.

Common side-effects

The most common side-effects of aspirin include indigestion and irritation of the stomach. Between 1 in 10 and 1 in 100 people will experience these side-effects. Aspirin can also make you more prone to bruising.

Un-common side-effects

Aspirin can cause minor bleeding from the stomach or bowel. It is very important to tell your study doctor or nurse or GP if you have any dark or black stools or any vomiting of blood. This is uncommon (between 1 in 100 and 1 in 1000 people will experience it). Aspirin can also cause severe bleeding, but this is rare and will affect between 1 in 1000 and 1 in 10,000 people.

Rare side-effects

Irritation of the stomach or bowel can cause a small break in the lining called an ulcer. It is

very important to tell your study doctor or nurse or GP if you have any dark or black stools or any vomiting of blood. Rarely, bleeding in the brain occurs. It is important to have your blood pressure checked regularly while you are taking part in the study and this will be done at each visit. Aspirin can rarely cause other areas of bleeding for example, nose bleeds or bleeding gums. Hypersensitivity reaction (allergic reaction) is also a rare side-effect. Rare side-effects will affect between 1 in 1000 and 1 in 10,000 people.

Very rare side-effects

Kidney and liver impairment are very rare side-effects of aspirin. Very rare side-effects affect less than 1 in 10,000 people.

Other side-effects

Some people have experienced tinnitus (ringing sound in ears) when taking aspirin. Some recent evidence has suggested that a condition called macular degeneration (age related loss of sight) may be more common in people taking aspirin.

Please tell your GP or study doctor as soon as possible if you become concerned about any potential side-effects at any stage, or if you are concerned about any medical problems you are experiencing. For a more detailed list of possible side-effects, please see the patient information leaflet provided with your medication.

If you become pregnant or decide you want to during the study, please inform your study doctor or nurse as there are risks associated with taking aspirin during pregnancy.

6 What are the possible benefits and disadvantages of taking part?

What are the possible benefits of taking part in this study?

We hope that you will be helped by taking part in this study, but we can't guarantee this. However, the information we get from this study will help us to improve future treatments for people like you who have had treatment for cancer and help us find out more about the overall healthcare benefits that aspirin might provide such as preventing heart disease.

What are the possible disadvantages and risks of taking part in this study?

You might experience side-effects from the treatment that you take in this study. Side-effects of aspirin are listed in section 5.
You will be asked to have a blood test before joining the study and then asked for your permission to have additional blood tests during the study.

You may also be asked to have some extra appointments at the hospital if you take part in the study.

During the study, you will not be able to take drugs such as ibuprofen or Nurofen (non-steroidal anti-inflammatory drugs) on a regular basis.

If you have private medical insurance or require travel insurance, your policy may be affected. You should check this with your insurance provider.

7 Samples and genetic tests

Everybody that participates in this study will be asked to donate samples which may include small samples of blood, urine and tissue from their cancer. We would like to collect samples from everybody participating in the study, even if their study medication is stopped because it allows us to study the side-effects of aspirin.
If you choose not to give permission for this you can still take part in the study.

What samples will I be asked to donate?

Cancer samples: samples of your cancer may have been stored in the hospital pathology laboratory. If you decide to take part in this study, we will ask your permission to retrieve your samples. You will **not** be asked to have any additional samples taken for this to happen.

Blood samples: we will ask your permission to take a small amount of blood when you register for the study. We will ask your permission now to do this. This part of the study is entirely optional and if you do not give your permission for this, you can still take part in the main study.

What will happen to samples I give?

Your donated samples will be stored in a laboratory for future research on the anti-cancer effects of aspirin and other projects aimed at improving outcomes for cancer patients.

Any research using your donated samples would only be carried out after an independent research ethics committee has approved it.

Will any genetic tests be done?

Depending on your cancer type and your hospital, you may have routine genetic tests done. You will receive personal results from these tests. Your study doctor can tell you more about these tests.

In the future, cancer researchers would like to use the blood and cancer samples that you donate (including your DNA) for separately approved research to help find out how genetics influence the risk of cancer and responses to treatments (including aspirin). You will not receive any personal results from these non-routine genetic tests unless we discover genetic information which has significant implications for your ongoing care, your future health or for that of your family. If this happens, we will contact you or the doctors looking after you with this information.

8 More information about taking part

Do I have to take part in the Add-Aspirin study?

No, it is up to you to decide whether or not to take part. If you decide to take part, we will ask you to sign a form to give your consent before the 8 week run-in period and again if you decide to continue in the study after the run-in period and to be randomised to one of the three treatments.

You can stop taking part in the study at any time and without giving a reason. You can also decide not to take part. This will not affect the standard of care you receive. If you do decide to stop taking part, please discuss this with your doctor.

If you decide to stop taking your study tablets, we would like to continue to collect some

information about you. This will help us to test whether aspirin does stop cancer coming back. This is important, as it helps us to ensure that the results of the study are reliable.

If you decide not to take part in this study, you will continue to have your regular check-ups and any other medication that you are receiving (for example, hormone treatment if you have had breast or prostate cancer), without taking the study medications.

Who is organising and funding the study?

University College London (UCL) has overall responsibility for this study. It is organised by the Medical Research Council Clinical Trials Unit (MRC CTU at UCL), which has run studies of this kind for many years. MRC CTU at UCL will manage the study and will collect and analyse the information. You can find out more about the MRC CTU at UCL here: www.ctu.mrc.ac.uk.

This study is being paid for by the charity Cancer Research UK, the National Institute for Health Research's Health Technology Assessment Programme (part of the UK Department of Health) and the MRC CTU at UCL.

Bayer Pharmaceuticals have supplied the aspirin tablets and placebo tablets for this study.

You will not be paid for taking part in this study. Your doctor is not receiving any money or other payment for asking you to take part in the study.

Who has reviewed the Add-Aspirin study?

The study has been reviewed by international scientists on behalf of the funders. It has been authorised by the regulatory body in the UK, Medicines and Healthcare products Regulatory Agency (MHRA), as well as by South Central - Oxford C Research Ethics Committee and your hospital's Research and Development office.

What will happen to information about me collected during the study?

If you agree to take part in the study, your doctor will send information about you, your cancer and your progress to the MRC CTU. This information will be put into a computer and analysed by Add-Aspirin researchers. With your permission, we will also link to your details at the NHS Central Register (NHSCR), so we can check your health status if you lose touch with your study doctor or stop visiting the hospital. To do this, we will need to keep your name and NHS number on file, but these will be kept separately from other information about you. Some participants may be asked to send a health update directly to the MRC CTU. You do not have to take part in this aspect of the study if you do not wish.

Also, if you agree to take part in the study, your medical records may be looked at by selected hospital staff or the lead doctor for the study (or his/her nominee).

Results from the study and any future research will be published but will be anonymous.

We will follow all legal requirements to make sure that all information about you is treated in confidence.

If you take part in this study, we will also tell your GP that you are taking part in this study so that s/he is aware that you might be taking aspirin.

We would also like to keep you updated with information about the study. If you would like us to send you information, we will take your contact details and keep them separately from other information about you. You do not

have to give us your contact details if you do not want us to send you updates.

What will happen to the results of the Add-Aspirin study?

If you give us permission, we will contact you to tell you the results of this study when it is completed. We will also publish a summary of the results on the study website: www.AddAspirinTrial.org and in a medical journal, so that other doctors can see them. You can ask your doctor for a copy of any publication. Your identity and any personal details will be kept confidential. No named information about you will be published in any report of this study.

What if new information becomes available during the course of the study?

Sometimes during a study, new information becomes available about the medicines that are being studied. An independent committee will look at any new information and will also look at the data collected so far in the study and decide if any changes are needed. If this happens, your doctor will tell you about it and discuss whether you want to continue in the study. If you decide to stop taking part in the study, your doctor will arrange for your care to continue.

Also, on receiving new information or because of a change in your health status, your doctor might consider that it is in your best interests to stop taking part in the study. Your doctor will explain the reasons and arrange for your care to continue.

What if something goes wrong?

If you have any concerns about the way you have been approached or treated during the study, or wish to complain, please use the normal NHS complaints process.

If you are harmed by taking part, or if you are harmed due to someone's negligence, then you may be able to take legal action.

9 Contacts for further information

If you want further information about the study, contact your study doctor or nurse (see below).
<<Insert address and telephone number of study doctor and/or nurse>>

You can also find information about the study on the following websites:
www.AddAspirinTrial.org
www.ctu.mrc.ac.uk
www.cancerresearchuk.org/cancer-help

Thank you for taking the time to consider taking part in this study.

APPENDIX II – CONSENT FORM (UK)

(To be presented on local headed paper) Version 4.0, 11-Nov-2014

Add-Aspirin Clinical Trial

Consent Form
To be completed at registration

Centre Name: .....

Patient ID Number: | | | | | | | | | |

Name of Researcher taking consent: ..... Initial boxes to agree

1. I confirm that I have read and understood the information sheet for the Add-Asprin research study (version 4.0, 11-Nov-2014) and have been given a copy to keep. I have had the opportunity to ask questions about the study and discuss it with my doctor and I have received satisfactory answers to all of my questions. ☐

2. I understand that sections of any of my medical notes may be looked at by responsible individuals from the Medical Research Council (MRC) Clinical Trials Unit (CTU) or from regulatory authorities where it is relevant to my taking part in this research study. I give permission for these individuals to have access to my records, but understand that my confidentiality will be maintained. ☐

3. I understand that my GP will be informed of my participation in the research study. ☐

4. I understand that I may not benefit directly by participating in this study but that the research may help people with this condition in the future. ☐

5. I understand that my participation in all aspects of this study is voluntary and that I am free to withdraw from the study at any time, without giving any reason and without my medical care or legal rights being affected. ☐

6. I agree to take part in the above study. ☐

The following parts of the study are optional – you can decide about each one separately but still take part in the study.

7. In order to follow up on my health status after my participation in the study, I give permission for my name and NHS number (CHI number in Scotland) to be used to obtain information about my health status, for example, from records held by the NHS and maintained by the NHS Information Centre and the NHS Central Register or any applicable NHS information system. I understand that this will take place even if I am not randomised after registration. ☐

Patient ID Number: | | | | | | | | | |

Initial boxes to agree

8. I give permission for a copy of this consent form to be sent to the MRC CTU (where it will be logged before being destroyed), to show that my consent was given. ☐

9. I give permission for my contact details to be used to contact me directly with information and updates about the progress of the study and the final results of the study. ☐

10. I give permission for my stored cancer samples to be made available for future research including DNA analysis. ☐

11. I give permission for a blood sample to be taken when I register for the study and give permission for this to be made available for future research, including DNA analysis. ☐

12. I understand that my samples may be used in research, including non-routine genetic tests. There will be no individual results available from this research unless they affect my clinical care, whether for this cancer, or in regards to other serious or life-threatening medical conditions for me or my family. ☐

13. I understand that my anonymised samples and/or anonymised data (including data collected through NHS information systems may be used in future research, and this may be carried out by researchers other than UCL. Studies using data and/or samples collected in the trial will only take place after scientific and ethical review. ☐

Name of Participant (BLOCK CAPITALS)	Date (dd/mm/yyyy)	Signature
Name of Researcher (BLOCK CAPITALS)	Date (dd/mm/yyyy)	Signature
Name of Person asking for consent (if different from researcher) (BLOCK CAPITALS)	Date (dd/mm/yyyy)	Signature

To be completed *after* run-in period and *prior to* randomisation:

15. I have completed the run-in period and now give my permission to continue in this study and be randomised. ☐

Name of Participant (BLOCK CAPITALS)	Date (dd/mm/yyyy)	Signature
Name of Researcher (BLOCK CAPITALS)	Date (dd/mm/yyyy)	Signature
Name of Person asking for consent	Date (dd/mm/yyyy)	Signature

(if different from researcher)
(BLOCK CAPITALS)

Please sign 1 copy. The study nurse (or doctor) will make another three copies:

- The original will be kept by the hospital with your notes
- 1 copy will be for you to keep
- 1 copy will be kept by the study doctor
- 1 copy will be sent to the MRC CTU (if box 8 is initialled), but your name will not be included

APPENDIX III – GP LETTER (UK)

(To be presented on local headed paper) Version 4.0, 11-Nov-2014

Add-Aspirin Clinical Trial ISRCTN#

Taking daily aspirin after early stage cancer treatment
GP Letter

Patient ID Number: | | | | | | | | | |

Dear Dr ……..

Your patient, ……..
(Date of birth dd/mmm/yyyy), has consented to participate in the Add-Aspirin clinical trial.

Add-Aspirin is a double-blind, placebo-controlled, randomised trial assessing the addition of aspirin after standard primary therapy in early stage common solid tumours. Participants are allocated to receive either 100mg aspirin daily, 300mg aspirin daily or a matched placebo daily for five years.

Please find enclosed a copy of the patient information sheet for this trial and a list of drugs to be avoided. This has also been given to your patient. It is important that participants do not regularly take any other medication that contains aspirin or NSAIDs but short term NSAID use is allowed for a maximum of two weeks where no alternative is available. Please note that participants have been advised that aspirin increases the risk of serious bleeding and to seek urgent medical advice if they have any concerns.

Participants will have their blood pressure checked at each trial visit. Those found to have hypertension should have their blood pressure managed according to standard practice.

In the event that emergency unblinding is required, the study doctor should be contacted. However, if this is not possible, and the emergency is clearly not related to the trial medication, the case may be appropriately managed by assuming that the participant is receiving the highest possible dose of active product (300mg aspirin), without the need for unblinding.

You will be kept up to date with your patient's progress but if you have any concerns or questions regarding this study please contact the responsible doctor:

Dr ……at …….. (Hospital)

Tel: ……

Kind regards,

Name
Position

APPENDIX IV – MEDICINES NOT PERMITTED DURING TRIAL TREATMENT

The following lists are not exhaustive and clinical judgement should be exercised. For further information please refer to the British National Formulary or local equivalent.

Anti-coagulants:	Warfarin Acenocoumarol Phenindione Dabigatran Unfractionated Heparin Low molecular weight heparin[1] Rivaroxaban Apixaban Argatroban	**Anti-platelets:**	Clopidogrel Dipyridamole Prasugrel Ticagrelor Abciximab Tirofiban Eptifibatide Epoprostenol fondaparinaux
LONG-TERM NSAIDS:[2]	Ibuprofen Naproxen Diclofenac Acelofenac Fenoprofen Flurbiprofen Ketoprofen Dexketoprofen Tiaprofenic acid Etodolac Indomethacin Meloxicam Tenoxicam Nabumetone Phenylbutazone Ketorolac Piroxican Sulindac Tolfenamic acid Celecoxib etoricoxib	**Aspirin:** (including over the counter)	Nu-seals Anadin Beechams powders Alka-seltzer Disprin Codis 500
		Others:	Methotrexate Long-term corticosteroids[3] (e.g. dexamethasone, prednisolone, hydrocortisone)

1. Low molecular weight heparin at a prophylactic dose for inpatient thromboembolism is permitted.

2. Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided wherever possible but short term intermittent NSAID use is allowed. NSAIDs should not be co-administered with the trial treatment for more than 2 consecutive weeks). Paracetamol can be considered as an alternative analgesic and is permitted within the trial.

3. Short term intermittent systemic corticosteroids are permitted (and are likely to prescribed alongside chemotherapy) however longer term use (longer than 2 continuous weeks) is not permitted.

APPENDIX V – COMMON TOXICITY CRITERIA

The following table details the grading and definitions of some of the known side-effects and should be used when reporting SAEs and describing toxicities. For the complete list of toxicities, please refer to CTCAE v4.

	GRADE				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Gastro-oesophageal reflux disease	Mild symptoms; intervention not included	Moderate symptoms; medical intervention indicated	Severe symptoms; surgical intervention indicated	-	-
Definition: A disorder characterised by reflux of the gastric and/or duodenal contents into the distal oesophagus. It is chronic in nature and usually caused by incompetence of the lower oesophageal sphincter, and may result in injury to the oesophageal mucosal. Symptoms include heartburn and acid indigestion.					
Lower gastrointestinal haemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterisation indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterised by bleeding from the lower gastrointestinal tract (small intestine, large intestine and anus).					
Upper gastrointestinal haemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterisation indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterised by bleeding from the upper gastrointestinal tract (oral cavity, pharynx, oesophagus and stomach).					
Tinnitus	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterised by noise in the ears, such as ringing, buzzing, roaring or clicking.					
Intracranial haemorrhage	Asymptomatic; clinical or diagnostic observations only; intervention not required	Moderate symptoms; medical intervention indicated	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterised by bleeding from the cranium.					
Haematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL	Gross haematuria; transfusion, IV medications or hospitalisation indicated; elective endoscopic, radiologic or operative intervention indicated; limiting self care ADL	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death

Definition: A disorder characterised by laboratory test results that indicate blood in the urine.					
Eye disorders - Other	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately sight-threatening; hospitalisation or prolongation of existing hospitalisation indicated; disabling; limiting self care ADL	Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye	-
Abdominal distension	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe discomfort; limiting self care ADL	-	-
Definition: A disorder characterised by swelling of the abdomen					
Allergic reaction	Transient flushing or rash drug fever <38˚C; intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDs, narcotics); prophylactic medications indicated for ≤24hrs	Prolonged (e.g. not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalisation indicated for clinical sequelae (e.g. renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterised by an adverse local or general response from exposure to an allergen					
Anaphylaxis	-	-	Symptomatic bronchospasm with or without urticarial; parenteral intervention indicated; allergy-related oedema/angio-oedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterised by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.					

APPENDIX VI – BREAST TUMOUR STAGING

Anatomic stage/prognostic groups			
Stage 0	Tis	N0	M0
Stage IA	T1*	N0	M0
Stage IB	T0	N1mi	M0
	T1*	N1mi	M0
Stage IIA	T0	N1**	M0
	T1*	N1**	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

*T1 includes T1mi.

**T0 and T1 tumours with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB.

From the 7th edition of the AJCC TNM staging manual.

APPENDIX VII – COLORECTAL TUMOUR STAGING GUIDELINE

TNM staging		Dukes' Stage
Tis, N0, M0	Stage O	
T1, N0, M0 T2, N0, M0	Stage I	A
T3, N0, M0	Stage II A	B
T4, N0, M0	Stage II B	B
T1, N1, M0 T2, N1, M0	Stage III A	C
T3, N1, M0	Stage III B	C
T4, N1, M0	Stage III B	C
T1, N2, M0 T2, N2, M0 T3, N2, M0	Stage III C	C
T4, N2, M0	Stage III C	C
Any T, Any N, M1	Stage IV	

From the 5th edition of the AJCC TNM staging manual.

APPENDIX VIII – GASTRIC TUMOUR STAGING

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
	T1	N1	M0
Stage IIA	T3	N0	M0
	T2	N1	M0
	T1	N2	M0
Stage IIB	T4a	N0	M0
	T3	N1	M0
	T2	N2	M0
	T1	N3	M0
Stage IIIA	T4a	N1	M0
	T3	N2	M0
	T2	N3	M0
Stage IIIB	T4b	N0	M0
	T4b	N1	M0
	T4a	N2	M0
	T3	N3	M0
Stage IIIC	T4b	N2	M0
	T4b	N3	M0
	T4a	N3	M0
Stage IV	Any T	Any N	M1

From the 7th edition of the AJCC TNM staging manual.

APPENDIX IX – OESOPHAGEAL TUMOUR STAGING

Squamous cell carcinoma					
Stage	T	N	M	Grade	Tumour location
0	Tis (HGD)	N0	M0	1, X	Any
IA	T!	N0	M0	1, X	Any
IB	T1	N0	M0	2-3	Any
	T2-3	N0	M0	1, X	Lower, X
IIA	T2-3	N0	M0	1, X	Upper, middle
	T2-3	N0	M0	2-3	Lower, X
IIB	T2-3	N0	M0	2-3	Upper, middle
	T1-2	N1	M0	Any	Any
IIIA	T1-2	N2	M0	Any	Any
	T3	N1	M0	Any	Any
	T4a	N0	M0	Any	Any
IIIB	T3	N2	M0	Any	Any
IIIC	T4a	N1-2	M0	Any	Any
	T4b	Any	M0	Any	Any
	Any	N3	M0	Any	Any
IV	Any	Any	M1	Any	Any

Adenocarcinoma				
Stage	T	N	M	Grade
0	Tis (HGD)	N0	M0	1, X
IA	T1	N0	M0	1-2, X
IB	T1	N0	M0	3
	T2	N0	M0	1-2, X
IIA	T2	N0	M0	3
IIB	T3	N0	M0	Any
	T1-2	N1	M0	Any
IIIA	T1-2	N2	M0	Any
	T3	N1	M0	Any
	T4a	N0	M0	Any
IIIB	T3	N2	M0	Any
IIIC	T4a	N1-2	M0	Any
	T4b	Any	M0	Any
	Any	N3	M0	Any
IV	Any	Any	M1	Any

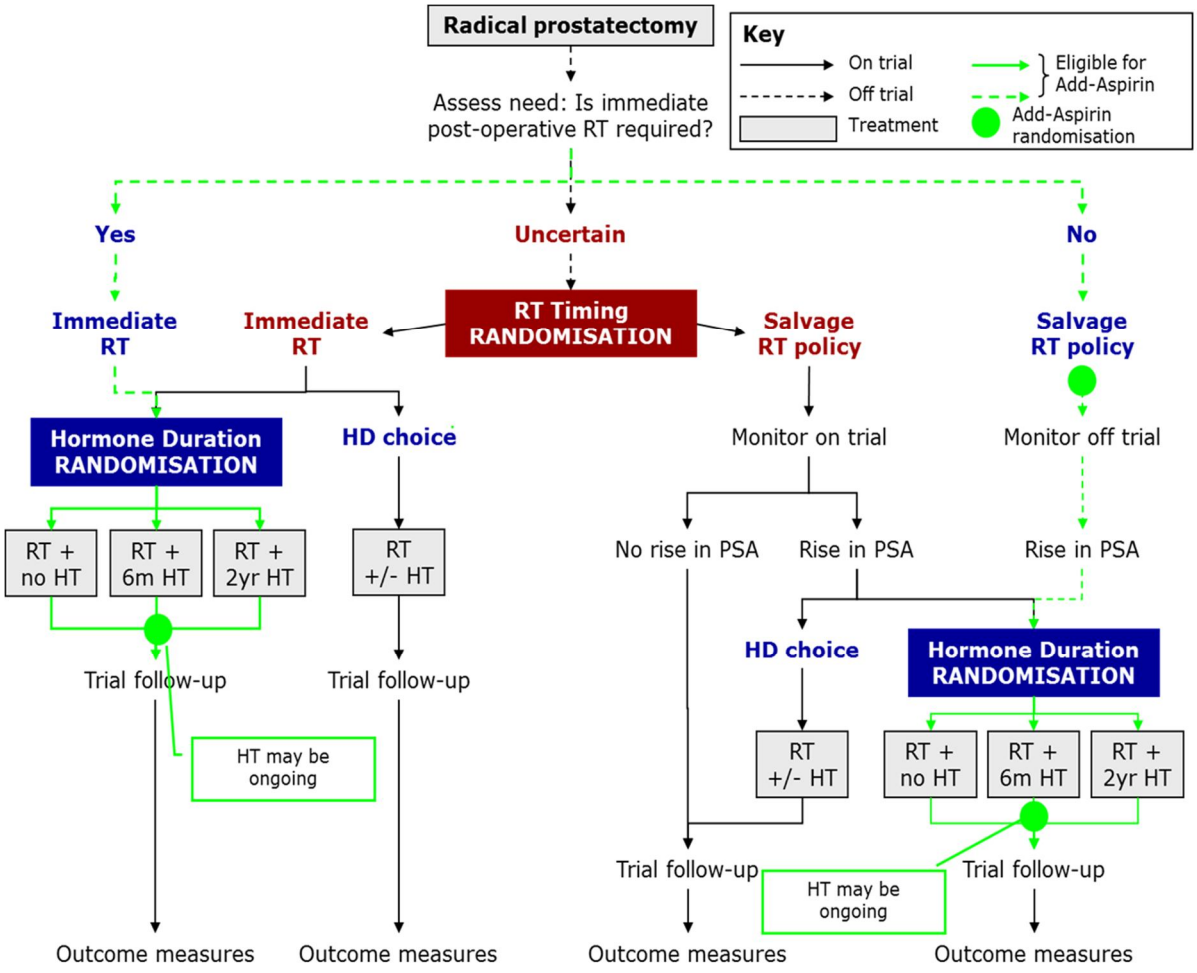
From the 7th edition of the AJCC TNM staging manual.

APPENDIX X – PROSTATE CANCER STAGING

Anatomic stage/Prognostic groups					
Group	T	N	M	PSA	Gleason
I	T1a-c	N0	M0	PSA<10	Gleason ≤6
	T2a	N0	M0	PSA<10	Gleason ≤6
	T1-2a	N0	M0	PSAX	Gleason X
IIA	T1a-c	N0	M0	PSA<20	Gleason 7
	T1a-c	N0	M0	PSA≥10<20	Gleason ≤6
	T2a	N0	M0	PSA≥10<20	Gleason ≤6
	T2a	N0	M0	PSA<20	Gleason 7
	T2b	N0	M0	PSA<20	Gleason ≤7
	T2b	N0	M0	PSAX	Gleason X
IIB	T2c	N0	M0	Any PSA	Any Gleason
	T1-2	N0	M0	PSA≥20	Any Gleason
	T1-2	N0	M0	Any PSA	Gleason ≥8
III	T3a-b	N0	M0	Any PSA	Any Gleason
IV	T4	N0	M0	Any PSA	Any Gleason
	Any T	N1	M0	Any PSA	Any Gleason
	Any T	Any N	M1	Any PSA	Any Gleason

From the 7th edition of the AJCC TNM staging manual.

APPENDIX XI – RADICALS AND ADD-ASPIRIN



APPENDIX XII – TRIAL MANAGEMENT GROUP AND COLLABORATORS

Gastro-oesophageal Cohort		
Dr Ruth Langley	Chief Investigator Lead Investigator – Gastro-oesophageal Cohort (UK)	London, UK
Dr Conjeevaram S Pramesh	Lead Investigator – India Lead Investigator – Gastro-oesophageal Cohort (India)	Mumbai, India
Dr Richard Hubner	Medical Oncologist – Gastro-oesophageal Cohort	Manchester, UK
Professor Janusz Jankowski	Gastroenterologist – Gastro-oesophageal Cohort	Plymouth, UK
Mr Tim Underwood	Surgeon – Gastro-oesophageal Cohort	Southampton, UK
Professor Anne Thomas	Medical Oncologist – Gastro-oesophageal Cohort	Leicester, UK
Breast Cohort		
Dr Alistair Ring	Lead Investigator – Breast Cohort (UK)	London, UK
Professor David Cameron	Lead Investigator – Translational Research Medical Oncologist – Breast Cohort	Edinburgh, UK
Professor Sudeep Gupta	Lead Investigator – Breast Cohort (India)	Mumbai, India
Colorectal Cohort		
Dr Richard Wilson	Lead Investigator – Colorectal Cohort	Belfast, UK
Dr Tim Iveson	Medical Oncologist – Colorectal Cohort	Southampton, UK
Professor Robert Steele	Surgeon – Colorectal Cohort	Dundee, UK
Prostate Cohort		
Professor Howard Kynaston	Lead Investigator – Prostate Cohort	Cardiff, UK
Dr Duncan Gilbert	Clinical Oncologist – Prostate Cohort	Brighton, UK
Mr Paul Cathcart	Surgeon – Prostate Cohort	London, UK
Cross-Study Collaborators		
Professor Mahesh Parmar	Director, MRC CTU	London, UK
Professor Peter Rothwell	Clinical Neurologist	Oxford, UK
Professor Carlo Patrono	Pharmacologist	Rome, Italy

Professor Sir John Burn	Clinical Geneticist	Newcastle, UK
Dr Michael Peake	Clinical Lead, National Cancer Intelligence Network	London, UK
Dr David Adlam	Cardiologist	Leicester, UK
Participant Representatives		
Lindy Berkman	Participant Representative, NCRI Consumer Liaison Group	UK
Mairead MacKenzie	Participant Representative, Independent Cancer Patient Voices	UK
Vandana Gupta	Participant Representative, VCare	India
Translational Research Collaborators		
Professor Malcolm Mason	Translational Research Co-investigator	Cardiff University
Professor John Chester	Translational Research Co-investigator	Cardiff University
Dr Alison Parry-Jones	Translational Research Co-investigator	Cardiff University
Professor Frank Carey	Translational Research Co-investigator	University of Dundee
Professor Simon Herrington	Translational Research Co-investigator	University of Dundee
Dr Ian Forgie	Translational Research Co-investigator	University of Dundee
MRC CTU at UCL		
Claire Murphy	Trial Manager	MRC CTU, UK
Laura Stevenson	Trial Manager	MRC CTU, UK
Ben Sydes	Data Manager	MRC CTU, UK
Sam Rowley	Statistician	MRC CTU, UK
Dr Fay Cafferty	Project Leader/Senior Statistician	MRC CTU, UK
Dr Chris Coyle	Trial Physician	MRC CTU, UK

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