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: **7.0**
Date: **21-Oct-2019**

MRC CTU ID:	**AA01**
ISRCTN #:	**74358648**
EudraCT #:	**2013-004398-28**
CTA #:	**31330/0006/001-0001**
REC #:	**14/SC/0171**
CTRI #:	**CTRI/2016/11/007469**

Authorised by:

Name:	Professor Ruth Langley
Role:	Chief Investigator, MRC Clinical Trials Unit Lead
Signature:	
Date:	21-Oct-2019
Name:	Professor Mahesh Parmar
Role:	Senior Statistician, Director, MRC Clinical Trials Unit at UCL
Signature:	
Date:	21-Oct-2019

GENERAL INFORMATION

This document was constructed using the Medical Research Council Clinical Trials Unit at UCL (MRC CTU at UCL) Protocol Template Version 4.0. It describes the Add-Aspirin trial, coordinated by the MRC CTU at UCL, 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 and guidelines.

SPONSORS

University College London (UCL) and the Tata Memorial Centre (TMC) are co-sponsors of the trial and have delegated responsibility for the overall management of the Add-Aspirin trial in the UK and Republic of Ireland to the MRC CTU at UCL, with some responsibilities in the Republic of Ireland delegated to Cancer Trials Ireland. In India, the Tata Memorial Centre assumes overall responsibility for management of the trial.
Queries relating to UCL co-sponsorship of this trial should be addressed to the Director of the MRC CTU at UCL (Professor Mahesh Parmar), Institute of Clinical Trials and Methodology, 90 High Holborn, 2nd Floor, London WC1V 6LJ, UK or via the Add-Aspirin Trial Manager. Queries relating to TMC co-sponsorship of the trial should be addressed to the Director of the Tata Memorial Centre (Dr RA Badwe), Dr E. Borges Marg, Parel, Mumbai – 400 012, India.

FUNDING

The Add-Aspirin trial is jointly funded by Cancer Research UK (CRUK) and the UK National Institute of Health Research (NIHR) Health Technology Assessment Programme (HTA). In India, the Sir Dorabji Tata Trust provides funding. The Add-Aspirin translational sample collection is funded by CRUK. The trial is coordinated and supported by the Medical Research Council Clinical Trials Unit at University College London (MRC CTU at UCL).

DRUG SUPPLIES

Bayer Pharmaceuticals AG has agreed to provide the Investigational Medicinal Products (IMPs). In India CIPLA Ltd is providing supplies of aspirin 100mg for the run-in period.

AUTHORISATIONS AND APPROVALS (UK)

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. For details of approvals in the Republic of Ireland please refer to the Delegation of Roles and Responsibilities Summary.

TRIAL REGISTRATION

Add-Aspirin is registered with the International Standard Randomised Controlled Trial Number (ISRCTN74358648) Clinical Trials Register and with the Clinical Trial Registry of India (CTRI/2016/11/007469)

CLINICAL CENTRES

Add-Aspirin is open to centres in every Cancer Research Network (CRN) throughout the UK. It is also open to a number of centres in India and in the Republic of Ireland. Specific arrangements for the conduct of the trial in India and the Republic of Ireland (where these differ from the UK) are covered in country specific appendices. Over time, centres in other countries may also join the trial.

PARTICIPANT REGISTRATIONAND RANDOMISATION

REGISTER PARTICIPANTS ONLINE AT (UK, India and Republic of Ireland):
www.addaspirintrial.org

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

INDIA & REPUBLIC OF IRELAND - RANDOMISE PARTICIPANTS ONLINE:
www.addaspirintrial.org

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 – UK and Republic of Ireland
Within 24 hours of becoming aware of an SAE, please send a completed SAE and Notable Event Form to the MRC CTU by fax:
Fax: +44 (0)20 7670 4818
or send via galaxkey to the trial mailbox:
Galaxkey: mrcctu.add-aspirin@ucl.ac.uk

SERIOUS ADVERSE EVENT REPORTING – INDIA
Within 24 hours of becoming aware of an SAE, please send a completed SAE and Notable Event Form to the CRO:

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 4892 or +44(0)207670 4759 or +44(0)20 7670 4906
Email: mrcctu.add-aspirin@ucl.ac.uk

TRIAL ADMINISTRATION

Please direct all queries to the Trial Managers at the MRC CTU at UCL in the UK or to the Clinical Research Organisation (CRO) in India; Contact details for India will be provided in a country specific appendix. 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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CHIEF INVESTIGATOR

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TUMOUR SITE-SPECIFIC LEAD INVESTIGATORS

UK

Lead Investigator – Breast Cohort(UK)	Dr Alistair Ring	London, UK
Lead Investigator – Colorectal Cohort	Professor Richard Wilson	Belfast, UK
Lead Investigator – Gastro-oesophageal Cohort	Professor 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	Professor C S Pramesh	Mumbai, India
Lead Investigator – Breast Cohort (India)	Professor Sudeep Gupta	Mumbai, India
Lead Investigator – Colorectal Cohort (India)	Dr Avanish Saklani	Mumbai, India
Lead Investigator – Gastro-oesophageal Cohort (India)	Professor C S Pramesh	Mumbai, India
Lead Investigator – Prostate Cohort (India)	Dr Ganesh Bakshi	Mumbai, India

REPUBLIC OF IRELAND

Lead Investigator – Breast Cohort (Republic of Irelend)	Dr Janice Walshe	Republic of Ireland
Lead Investigator – Colorectal Cohort (Republic of Irelend)	Dr Greg Leonard	Galway, Republic of Ireland
Lead Investiator – Gastro-Oesophageal Cohort (Republic of Irelend)	Dr Seamus O'Reilly	Republic of Ireland
Lead Investigator – Prostate Cohort (Ireland)	Professor Raymond McDermott	Republic of Ireland

For full details of all co-investigators please see Appendix XIII.

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	6.0
Date	25-Jul-2019
ISRCTN #	74358648
CTRI #	CTRI/2016/11/007469
EudraCT #	2013-004398-28
CTA #	31330/0006/001-0001
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 xi. 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 tumour-specific analyses. The trial incorporates an open-label, active run-in period. A feasibility phase, based on data from the run-in, has now been completed. Data from n=2253 participants suggested that aspirin was acceptable and well-tolerated after radical therapy. The trial continues as planned.[1] The trial has been designed such that additional randomised comparisons may be added over time, subject to obtaining the appropriate funding and approvals. Any such addition would be implemented via a protocol amendment once all relevant regulatory and ethical approvals were obtained. This model provides efficiencies at a number of levels when compared with initiation of a new study.
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.

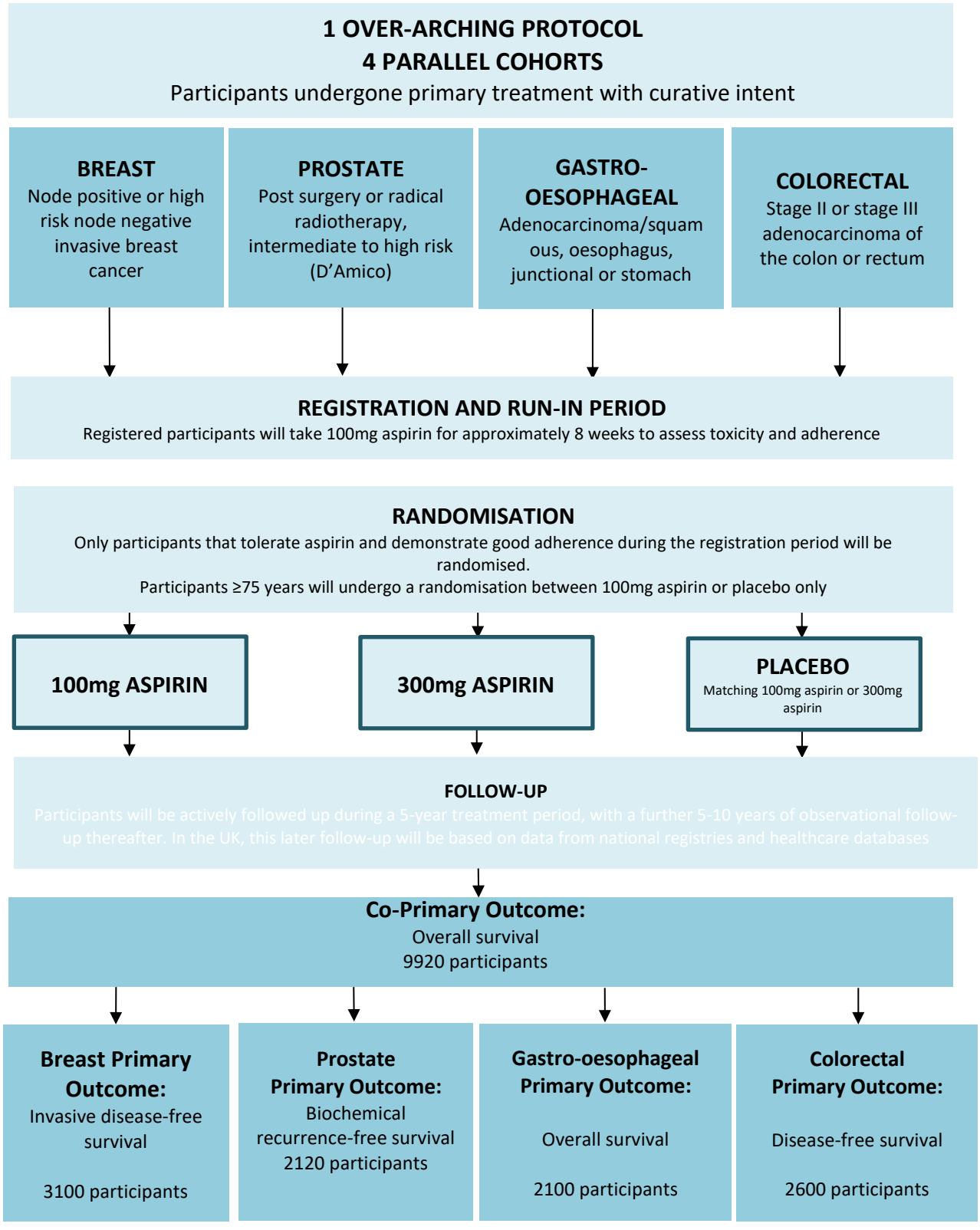
SUMMARY INFORMATION TYPE	SUMMARY DETAILS
Type of participants to be studied	Participants who have undergone potentially curative treatment (surgery or other radical treatment), including any standard neo-adjuvant or adjuvant therapy for breast, colorectal, gastro-oesophageal or prostate cancer or have 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. All participants will take open label 100mg aspirin daily for a run-in period of approximately 8 weeks prior to randomisation.
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, as well as 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 in the UK can be randomised by phone (+44 (0)20 7670 4777). Eligible participants in India or Republic of Ireland can be randomised via the trial website. 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.
Estimated Number of participants to be randomised (UK,India and Republic of Ireland)	Total: 9920 participants Breast: 3100 participants Colorectal: 2600 participants Gastro-oesophageal: 2100 participants Prostate: 2120 participants

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
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. All participants will be actively followed up for at least 5 years after randomisation. In the UK, after this time, long-term passive follow-up data will be obtained from routinely-collected healthcare databases for at least 10 further years. In India and the Republic of Ireland, where follow-up via routine data sources is not currently possible, participants will be contacted on an annual basis for a further 5 years. Participants in Republic of Ireland will be actively followed 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 once all participants have been followed up for 10 years.
POLEM trial collaboration	POLEM (EudraCT Number: 2017000370-10) is a UK, phase III randomised study assessing Avelumab plus fluoropyrimidine-based chemotherapy as adjuvant treatment for stage III dMMR or POLE exonuclease domain mutant colon cancer. Add-Aspirin UK colorectal centres are encouraged to screen patients for entry into the POLEM trial, and subsequent entry into Add-Aspirin. For further details please seen Appendix XIV.
Ancillary studies/sub studies	▪ Adherence in a sub-set of UK participants will be assessed by measuring thromboxane B_2, a product of platelet aggregation, which will provide an indicator of cyclooxygenase activity. ▪ Blood, urine 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 in the UK 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 aimed at improving trial conduct.
Co-Sponsors	University College London for the UK & Republic of Ireland University College London and Tata Memorial Centre (co-sponsors) for India

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
Funders	▪ Cancer Research UK ▪ National Institute Health Research (NIHR) Health Technology Assessment Programme (HTA, UK) ▪ Sir Dorabji Tata Trust (India) ▪ MRC Clinical Trials Unit at UCL ▪
Drug supply	▪ Bayer Pharmaceuticals AG has agreed to provide the placebo and active drug for the blinded phase (IMPs) and aspirin for the run-in period in the UK and Republic of Ireland. ▪ M/s CIPLA Ltd. has agreed to provide aspirin for the run-in period in India. ▪ Blinded drug and run-in drug for the UK and Republic of Ireland is packaged and distributed by Alcura

TRIAL SCHEMA

Figure 1. Trial Design



TRIAL ASSESSMENT SCHEDULE

The trial assessment schedule for each cohort, detailed on subsequent pages, is aligned with standard practice where possible to ensure the trial can be implemented easily. However, this is balanced with the need to ensure appropriate monitoring of patients on trial treatment and assessment of outcome measures.

Flexibility of Schedules and Follow Up:

To allow for variations in standard practice across sites, the following are permitted:

- Consent can be taken by research nurses, where delegated by the local Principal Investigator (PI), in the UK only.
- Follow-up can be led by a nurse member of the research team provided:
    - Appropriate clinical support is available
    - In the event of any adverse events, toxicities or other concerns, the participant will be seen by a doctor
- Follow-up at each time point should be conducted +/- 2 weeks from the date of randomisation wherever practically possible.
- Cognitive assessments (UK and Republic of Ireland only):
    - Can be performed over the telephone where no visit is planned
    - Can be administered by a non-clinical staff member (e.g. Data Manager)
- Routine imaging examinations and blood tests should be used when performed within in the specified timelines (see below) where available. Imaging examinations and blood tests do not need to be trial specific.
- Imaging examinations can be performed within +/-6 months from scheduled assessment point. Additional imaging examinations should be performed if clinically indicated.
- Where a visit is additional to local standard care, assessments can be conducted over the phone provided:
    - The protocol schedule is followed, including blood tests
    - Appropriate measures for dispensing trial medications are made
- Weight should be assessed as part of clinic visits but can be omitted where telephone follow-up is planned (as above).
- Blood pressure checks must be performed at the registration and end of run-in visit, and thereafter should be performed at least annually whilst patients are on trial treatment. These assessments would normally be performed as part of clinic visits, but can be collected via the GP or home readings where telephone follow-up is planned.
- Breast cohort only: No imaging is needed in the case of bilateral mastectomy. Alternative follow-up imaging (such as MRI in younger patients) is acceptable in place of mammography..
- Colorectal cohort only: it is expected that at least two of the three scheduled surveillance colonoscopies are performed, provided that the whole colorectum is visualised in the peri-surgical period. The 5 year colonoscopy is mandatory.
- Colorectal cohort only (UK centres): If participant is also enrolled in POLEM, follow trial assessment schedules found in Appendix XIV (Section 5).

Timing of Blood Tests:

The table below shows the timelines in which blood samples need to be collected during the course of the trial:

Blood test	Timeframe prior to registration	Timeframe prior to randomisation	Timeframe prior to follow up visit
FBC, U&E, LFT, eGFR	4 weeks *	2 weeks*	4 weeks*
Fasting lipids	4 weeks (result not required at time of registration)	N/A	N/A
CEA (colorectal cohort only)	4 weeks	2 weeks (result not required at time of randomisation)	4 weeks
PSA (prostate cohort only)	4 weeks	2 weeks (result not required at time of randomisation)	4 weeks
CRP	4 weeks (result not required at time of registration)	N/A	4 weeks
Whole blood sample for translational research	4 weeks	N/A	N/A

*For patients who have completed chemotherapy, a FBC result should be taken between the last day of the last cycle of chemotherapy (e.g. day 21 of a 3-week cycle) and the trial visit. For patients with ongoing chemotherapy, a FBC should be taken between the most recent administration of chemotherapy and the trial visit.

Please discuss any other queries with the MRC CTU at UCL trial team.

TRIAL ASSESSMENT SCHEDULE

BREAST COHORT

					MONTHS SINCE RANDOMISATION (EXCEPT WHERE INDICATED)											
		CRF NUMBER	PRIOR TO REGISTRATION	PRIOR TO RANDOMISATION (END OF RUN-IN PERIOD)	3	6	9	12	18	24	30	36	42	48	54	60
Main Assessments	Registration assessments[1]	**1bc, 3, 4, 16***	✓													
	End of run-in assessment[2]	**7**		✓												
	Follow-up assessments[3]	**8, 8bc**			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Imaging	Mammography[4]	**1bc, 8bc**	✓					✓		✓		✓		✓		✓
Intermittent assessments	VES-13 questionnaire[5] (65≥ years at registration)	**5**	✓													✓
	Cognitive assessment[5]	**6**	✓					✓								✓
	International Physical Activity Questionnaire	**8**						✓								✓
Blood tests	FBC, LFT, U&E & eGFR	**3, 7, 8**	✓	✓		✓		✓		✓		✓		✓		✓
	C-Reactive Protein (CRP)	**3, 8**	✓			✓		✓								
	Fasting lipid profile	**3**	✓													
Other tests	Tumour and blood sample to be stored in bio-bank[6, 7]	**2**	✓													
	Urine sample to be stored in bio-bank[6,] **(selected UK centres only)**	**2a**	✓	✓	✓											

1 Registration assessments include: eligibility, co-enrolment (*if applicable), blood pressure, height, weight, blood results, concomitant medication and comorbidities.
2 End of run-in assessments include: symptoms and toxicity, adherence, blood pressure.
3 Follow-up assessments include: symptoms and toxicity, adherence, blood pressure, weight, concomitant medication.
4 Diagnostic mammogram can be used for baseline scan provided that the mammogram is bilateral. No imaging is needed in the case of bilateral mastectomy. Alternative follow-up imaging (such as MRI in younger patients) is acceptable.
5 UK and RoI only
6 Where participants have given their consent.

[7] **RoI:** samples processed and stored locally at sites. **India:** Tumour blocks will be collected at all sites and sent for storage at TMC; blood sample collection is only applicable at TMC.

COLORECTAL COHORT (FOLLOW TRIAL ASSESSMENT SCHEDULE FOUND IN APPENDIX XIV SECTION 6 IF ENTERED POLEM TRIAL)

					MONTHS SINCE RANDOMISATION (EXCEPT WHERE INDICATED)											
		CRF NUMBER	PRIOR TO REGISTRATION	PRIOR TO RANDOMISATION (END OF RUN-IN PERIOD)	3	6	9	12	18	24	30	36	42	48	54	60
Main assessments	Registration assessments[1]	**1cc, 3, 4, 16***	✓													
	End of run-in assessment[2]	**7**		✓												
	Follow-up assessments[3]	**8, 8cc**			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Imaging and procedures	CT (chest, abdomen, pelvis)[4]	**1cc, 8cc**	✓					✓		✓						✓
	Colonoscopy[4, 5, 6]	**1cc, 8cc**	✓					✓			✓					✓
Intermittent assessments	VES-13 questionnaire[7] (65≥ years at registration)	**5**	✓													✓
	Cognitive assessment[7]	**6**	✓					✓								✓
	International Physical Activity Questionnaire	**8**						✓								✓
Blood tests	CEA test	**1cc, 7, 8cc**	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	FBC, LFT, U&E & eGFR[10]	**3, 7, 8**	✓	✓		✓		✓		✓		✓		✓		✓
	C-Reactive Protein (CRP)	**3, 8**	✓			✓		✓								
	Fasting lipid profile	**3**	✓													
Other tests	Tumour and blood sample to be stored in bio-bank[7,8, 9]	**2**	✓													
	Urine sample to be stored in bio-bank[8] **(selected centres only)**	**2a**	✓	✓	✓											

[1] Registration assessments include: eligibility, co-enrolment (*if applicable), blood pressure, height, weight, blood results, concomitant medication and comorbidities.
[2] End of run-in assessments include: symptoms and toxicity, adherence, blood pressure.
[3] Follow-up assessments include: symptoms and toxicity, adherence, blood pressure, weight, concomitant medication.
[4] Imaging examinations can be performed can be performed within +/- 6 months from scheduled assessment point.
[5] It is expected that at least two out of the three scheduled surveillance colonscopies, provided that the whole colorectum is visualised in the peri-surgical period. The 5 year colonscopy is mandatory.
[6] Diagnostic colonoscopy can be used for baseline.
[7] UK and RoI only

[8] Where participants have given their consent
[9] **RoI:** samples processed and stored locally at sites. **India:** Tumour blocks will be collected at all sites and sent for storage at TMC; blood sample collection is only applicable at TMC.

GASTRO-OESOPHAGEAL COHORT

					MONTHS SINCE RANDOMISATION (EXCEPT WHERE INDICATED)											
		CRF NUMBER	PRIOR TO REGISTRATION	PRIOR TO RANDOMISATION (END OF RUN-IN PERIOD)	3	6	9	12	18	24	30	36	42	48	54	60
Main assessments	Registration assessments[1]	**1gc, 3, 4, 16***	✓													
	End of run-in assessment[2]	**7**		✓												
	Follow-up assessments[3]	**8, 8gc**			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Intermittent assessments	VES-13 questionnaire[4] (65≥ years at registration)	**5**	✓													✓
	Cognitive assessment[4]	**6**	✓					✓								✓
	International Physical Activity Questionnaire	**8**						✓								✓
Blood tests	FBC, LFT, U&E & eGFR	**3, 7, 8**	✓	✓		✓		✓		✓		✓		✓		✓
	C-Reactive Protein (CRP)	**3, 8**	✓			✓		✓								
	Fasting lipid profile	**3**	✓													
Other tests	Tumour and blood sample to be stored in bio-bank[5, 6]	**2**	✓													
	Urine sample to be stored in bio-bank[5] **(selected centres only)**	**2a**	✓	✓	✓											

[1] Registration assessments include: eligibility, co-enrolment (*if applicable), blood pressure, height, weight, blood results, concomitant medication and comorbidities.
[2] End of run-in assessments include: symptoms and toxicity, adherence, blood pressure.
[3] Follow-up assessments include: symptoms and toxicity, adherence, blood pressure, weight, concomitant medication.
[4] UK and RoI only
[5] Where participants have given their consent.
[6] **RoI:** samples processed and stored locally at sites. **India:** Tumour blocks will be collected at all sites and sent for storage at TMC; blood sample collection is only applicable at TMC.

PROSTATE COHORT

					MONTHS SINCE RANDOMISATION (EXCEPT WHERE INDICATED)											
		CRF NUMBER	PRIOR TO REGISTRATION	PRIOR TO RANDOMISATION (END OF RUN-IN PERIOD)	3	6	9	12	18	24	30	36	42	48	54	60
Main assessments	Registration assessments[1]	**1pc, 3, 4, 16***	✓													
	End of run-in assessment[2]	**7**		✓												
	Follow-up assessments[3]	**8, 8pc**			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Intermittent assessments	VES-13 questionnaire[4] (65≥ years at registration)	**5**	✓													✓
	Cognitive assessment[4]	**6**	✓					✓								✓
	International Physical Activity Questionnaire	**8**						✓								✓
Blood tests	PSA	**1pc, 7, 8pc**	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	FBC, LFT, U&E & eGFR	**3, 7, 8**	✓	✓		✓		✓		✓		✓		✓		✓
	C-Reactive Protein (CRP)	**3, 8**	✓			✓		✓								
	Fasting lipid profile	**3**	✓													
Other tests	Tumour and blood sample to be stored in bio-bank[5, 6]	**2**	✓													
	Urine sample to be stored in bio-bank[5] **(selected centres only)**	**2a**	✓	✓	✓											

1 Registration assessments include: eligibility, co-enrolment (*if applicable), blood pressure, height, weight, blood results, concomitant medication and comorbidities.

2 End of run-in assessments include: symptoms and toxicity, adherence, blood pressure.

3 Follow-up assessments include: symptoms and toxicity, adherence, blood pressure, weight, concomitant medication.

4 UK and RoI only

5 Where participants have given their consent.

6 **RoI:** samples processed and stored locally at sites. **India:** Tumour blocks will be collected at all sites and sent for storage at TMC; blood sample collection is only applicable at TMC.

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
CTI	Cancer Trials Ireland
CTRI	Cancer Trials Registry of India
CTU	Clinical Trials Unit
DCIS	Ductal carcinoma in situ
DFS	Disease free survival

Abbreviation	Expansion
dMMR	DNA Mismatch Repair deficient
DNA	Deoxyribonucleic acid
DPA	(UK) Data Protection Act
DSMS	Drug Supply Management System
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
GDPR	General Data Protection Regulation
GI	Gastrointestinal
GP	General Practitioner
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HER2	Human epidermal growth factor
HPFS	Health Professional Follow-up Study
HR	Hazard ratio
HPRA	The Health Products Regulartory Authority
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IMP	Investigational medicinal product

Abbreviation	Expansion
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 at UCL	Medical Research Council Clinical Trials Unit at UCL
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
POLEM	Avelumab plus fluoropyrimidine-based chemotherapy as adjuvant treatment for stage III dMMR or POLE exonuclease domain mutant colon cancer: A phase III open label randomised study.
PPI	Proton pump inhibitor

Abbreviation	Expansion
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)
RMH	Royal Marsden Hospital
RR	Relative risk
SAE	Serious adverse event
SAR	Serious adverse reaction
SPC	Summary of Product Characteristics
SSA	Site-specific approval
SSI	Site-specific information
SUSAR	Suspected unexpected serious adverse reaction
TM	Trial Manager
TMC	Tata Memorial Centre
TMF	Trial master file
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected adverse reaction
UCL	University College London
U&E	Urea & electrolytes
UK	United Kingdom
ULN	Upper limit of normal

Abbreviation	Expansion
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,[2] with an estimated 14.1 million cases and 8.1 million deaths in 2012.[3] 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.[3]

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.[4] 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.[2,5] Thereis growing concern about the global economic burden of cancer and other chronic diseases.[6,7]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.[8]

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,[9] 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 arachidonic 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.[10] 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.[11]

Many of the downstream mediators of the Cox pathways are thought to be involved in the development and spread of malignancy.[12] 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[13-15] and the recent observational cohort studies[16,17] (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.[18]

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.[19] They may also protect circulating cancer cells from immune-mediated clearance by natural killer cells.[20] 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.[21]

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.[22] 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.[18] 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 mousemodels.[23] 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,[24] and if the tumours had mutated *PIK3CA,*[25] 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.[26] 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),[27] although again the numbers are small (14of 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[28-30] 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.[31] It inhibits activation of NF-kappa B,[32] which is thought to play a key role in tumour growth and invasion,[33] as well as promoting apoptosis,[34] inhibiting angiogenesis[35] and interacting with other cell cycle regulators and signalling pathways that are thought to influence the development and growth of malignancies.[36] *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.[36-38]

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[13-15,39]. 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.[14] 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.[39] 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).

A more recent analysis of some of these previous cardiovascular trials has considered the impact of body weight and aspirin dose – specifically pertaining to cardiovascular outcomes, but with some

data on cancer outcomes presented.[40] The findings suggested that the effects of aspirin – both in prevention of cardiovascular disease and prevention of colorectal cancer – may be weight dependent, with lower doses (75-100mg) only effective in individuals weighing <70kg, and higher doses (≥300mg) only effective for those >70kg. Thus, suggesting that a one-dose-fits-all approach for aspirin may not be appropriate. This requires further investigation, particularly in terms of cancer outcomes and in the adjuvant (as opposed to prevention) setting. The Add-Aspirin trial is well-placed to provide this evidence, since two different aspirin doses are being utilised across a broad spectrum of individuals.

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.[41] Since then there have been well over 100 case-control and cohort studies investigating the use of aspirin and cancer risk.[42] 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*.[42]

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,[43,44] 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)[45]. 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.[46] 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.[42] Observational studies have also shown improvements in survival with aspirin use after a diagnosis of breast cancer.[47-49] 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[48] (see table 2). 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.[50]

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.[41] 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).[42]

A role for aspirin in the secondary prevention of colorectal adenomas has been demonstrated. Observational studies have also shown improvements in survival with aspirin use after a diagnosis of

colorectal cancer.[16,17,24,51,52] 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.[53] More recently, the SeAFOod trial, assessed the use of Eicosapentaenoic acid and/or aspirin for the prevention of colorectal adenomas in individuals with a history of colorectal neoplasia. Whilst no impact of either treatment was seen on the primary outcome (the proportion of participants with any adenoma at 1 year colonoscopy), there was evidence of an effect of aspirin when considering total number of adenomas detected, as well as when considering adenomas by type/location.[54]

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).[13,14,55,56] 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.[45,46] The ongoing CAPP3 trial is assessing use of lower doses of daily aspirin for prevention of cancers associated with Lynch syndrome and will add further data to this field.[57]

Additional evidence of a potential role for aspirin as an adjuvant treatment for colorectal cancer comes from non-randomised studies (see table 2). 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.[24] 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),[17] 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).[16] Many of the *in vitro* studies investigating potential mechanisms by which aspirin has anti-cancer effects have been performed in colorectal cell lines.[58-60]

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.[61,62] 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.[42] More recently an observational study using data from the Eindhoven Cancer Registry has also shown improvements in survival with aspirin use after a diagnosis of gastro-oesophageal cancer.[63] 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)[14] with similar effects seen in both observational studies and the trial data for both gastric and oesophageal tumours.[64] 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) (see table 2). 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. Finally, the AspECT trial, which investigated use of a PPI (esomeprazole) and/or aspirin for improving outcomes in Barrett's oesophagus, suggested an improvement in the primary compositie outcome (death, oesophageal adenocarcinoma, and high-grade dysplasia) with the combination of treatments (vs low dose PPI, time ratio from accelerated failure time model, TR=1.59, 1.14-2.23, p=0.007), and a non-significant trend towards benefit with aspirin alone. Rates of serious toxicity

were low (1.0%). Although in the prevention setting, these results provide further evidence of a potential role for aspirin in gastro-oesophageal cancer, and of the safety of aspirin in this setting.[65]

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 prostatecohorthypothesis comes from published data from the multi-centre CaPSURE (Cancer of the Prostate Strategic Urologic Research) database(see table 2). 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 alarge 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).[63] More recently, an analysis of a large prospective cohort (*n*=8,427) found that post-diagnostic aspirin use in men with high risk non-metastatic prostate cancer resulted in a reduction in prostate cancer specific mortality (HR 0.60, 95% CI 0.37-0.97).[62]

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.[66] As in the other tumour sites, there are *in vitro* studies investigating the effects of aspirin in tumour cell lines [67,68] 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.[69] Recent results from the STAMPEDE trialindicated that celecoxib (a Cox-2 inhibitor) showed insufficient activity as an addition to lutenising hormone releasing hormone analogue (LHRHa) treatmentforlocally advanced and metastatic prostate cancer to warrant continued evaluation.[70] 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.[18]

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[24] *n=1,279*	CRC mortality HR 0.71 (0.53-0.95) All-cause mortality HR 0.79 (0.65-0.97)
	Bastiaannet*et al*. 2012[17] *n=4,481*	Overall survival (OS) RR 0.65 (0.50-0.84)
	McCowanet al. 2012[16]	CRC mortality HR 0.58 (0.45-0.75)

	n=2,990	Overall mortality HR 0.67 (0.57-0.79)
	Bains et al. 2016[52] *n=23,162*	CRC mortality HR 0.85 (0.79-0.92) Overall mortality HR 0.95(0.90-1.01).
Breast cancer (BC)	Nurses' Health Study, Holme s*et al*. 2010[48] *n=4,164*	BC mortality RR 0.36 (0.24-0.65) with daily use Overall mortality RR 0.54 (0.41-0.70) with daily use
	Fraser et al. 2014[49] *n=4,627*	BC mortality HR 0.42 (0.31-0.55) Overall mortality HR0.53(0.45-0.63)
Prostate cancer (PC)	Zaorsky *et al*. 2012[71] *n=2,051* (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[72] *n=5,995* (post-radical therapy)	PC mortality HR 0.43 (0.21-0.87)
	Jacobs et al. 2014[73] *n=7,118*	PC mortality HR0.60 (0.37-0.97) (high risk non-metastatic)
Gastro-oesophageal cancer	Liu*et al*. 2009[74] *n=1,600*	5-year OS aspirin 51.2%, placebo 41%, no tablet 42.3%. No HR/RR presented.
	Staalduinen et al. 2016[63] *n=560*	OS adjusted rate ratio 0.42 (0.30-0.57)

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.[75] 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.[76] 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).[77] 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).[78] A systematic review by the U.S Preventative Services Task force estimates an additional 1.39 (0.70 to 2.28) GI bleeding events and 0.32 (0.05 to 0.82) for haemorrhagic stroke events per 1000 person-years of aspirin exposure.[79] A number of measures are known to reduce the risk of serious adverse events for those receiving aspirin[80] 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.[18,55] 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 dailyfor 25 months (SD 12.5; range 0.8-60.6) and that, based on pill counts, adherence to therapy was good.[46,81]

Data from the feasibility stage of the Add-Aspirin trial are also now available. Run-in data from n=2253 participants (across the four different tumour cohorts) suggested that aspirin was well-tolerated after radical therapy, with good adherence and a low burden of toxicity. Safety data from the trial continues to be reviewed on a regular basis by the Independent Data Monitoring Committee.[1]

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),[14,55,56] 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.[16,82] 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).[24,83] 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.[83,84]

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

At the time of writing there are a number of complementary ongoing trials worldwide. These are largely focused on colorectal cancer, with trials in Asia (ASCOLT and APREMEC[85,86]), the Netherlands (ASPIRIN[87]), Norway (ASAC), Sweden (ALASCCA) and Switzerland (SAKK 41/13) – with ALASCCA and

SAKK 41/13 focusing on individuals with PIK3CA mutations.[88] There is also a similar breast cancer trial recruiting in the US (ABC).[89] Add-Aspirin complements these studies and has the additional benefits of simultaneously investigating the intervention across other disease sites and in a range of (socioeconomic) settings; as well as addressing the dose question.

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.

The trial has also been designed such that, over time, it might provide a platform for addition of new randomised comparisons, subject to obtaining funding and all of the relevant approvals. This model provides efficiencies at a number of levels when compared with initiation of a new trial.[90]

2 SELECTION OF CENTRES/CLINICIANS

The trial sponsor in the UK and Republic of Ireland, University College London (UCL), has overall responsibility for centre and Investigator selection. The trial sponsor in India, the Tata Memorial Centre (TMC) has responsibility for centre selection in India. The trial is run and managed by the MRC CTU at UCL with some operational roles delegated to the Tata Memorial Centre and a Contract 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 and Republic of Ireland 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 in the UK and India. 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 AND IRISH CENTRES

Initial participating centres in India and the Republic of Ireland have been selected prior to trial commencement in that country. Further centres may be selected based on similar criteria to sections 2.1.3 – 2.1.5, and the required documents must be completed. Centres will also be assessed by the CRO in India, or by Cancer Trials Ireland, in the Republic of Ireland, 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 at UCL. The MRC CTU at UCL 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 at UCL 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 at UCL 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 at UCL, 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 at UCL or by visiting the trial website.

3 SELECTION OF PARTICIPANTS

Providing potential participants with trial information (see Participant Information Sheet) 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. It can be helpful to identify potential participants early in the treatment pathway and track them through their primary treatment. 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). The trial website includes tips on recruitment.

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. The trial website provides answers to a number of common eligibility queries. 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 at UCL. 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 at UCL for patients in the UK and the Republic of Ireland 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.

UK centres participating in the colorectal cohort are also encourage to screen patients for the **POLEM trial** primary to considering them for Add-Aspirin. Full details of this process are provided in Appendix XIV.

3.1 BREAST COHORT INCLUSION CRITERIA

1. Men or women with histologically confirmed invasive breast cancer.
    a. Patients with synchronous unilateral breast tumours are eligible based on the characteristics of the highest staged tumour.
2. Patients have undergone complete primary invasive tumour excision with clear radial 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. If axillary surgery is to be undertaken, this should 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 groups:
    a. For patients *not* receiving neoadjuvant chemotherapy:
        i. Node positive, or,
        ii. 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
            - Prosignia score (PAM50) of >60

        -Patients are permitted to have had neoadjuvant endocrine therapy for up to 6 months, as long as final surgical pathology falls within one of the above two groups.
        -In the above definitions patients with micrometastases should be regarded as node positive. Patients with isolated tumour cells should be regarded as node negative.
    b. Patients who *have* received neo-adjuvant chemotherapy or radiotherapy must fall into one of the following 3 categories:
        i. Hormone receptor negative and HER2 negative tumour AND has not achieved a pathological complete response, or,
        ii. A HER2 positive tumour (any hormone receptor status) AND not achieved a pathological complete response, or,
        iii. A hormone receptor positive, HER2 negative tumour which is grade 3 AND has not achieved a pathological complete response.
7. Patients who received standard neo-adjuvant and/or adjuvant chemotherapy or radiotherapy are eligible. Timing of registration and starting run-in treatment in terms of the treatment pathway should be as described in section 4.2. (For confirmation of standard therapy, please contact MRC CTU at UCL).
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. A current list of trials where co-enrolment has been approved is available at www.addaspirintrial.org. For further details see section 4.4. If a potential participant is enrolled in a trial that is not listed, this should be discussed with the MRC CTU at UCL or TMC (India) 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 I 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*
    - *Previous regular use of aspirin ≥5 years agois acceptable. Any previous regular aspirin use within the last 5 years should be discussed with the MRC CTU at UCL who will advise on eligibility on a case-by-case basis*
    - *Current NSAID use is defined as taking any NSAID for more than a week in the preceding month*
    - *If investigators feel that these definitions may unfairly exclude a participant, this can be discussed with the MRC CTU at UCL 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 or with a single installation of intravesical chemotherapy or with BCG treatment.
    e. Other cancers where the patient has been disease-free for ≥15 years.
    f. Other cancers with very low potential for recurrence can be discussed with MRC CTU at UCL where eligibility will be considered on an individual basis.
10. Any other condition (physical or psychological) 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, 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 (with no evidence of residual or metastatic disease) unless the participant has been discussed with the MRC CTU at UCL and the Trial Management Group (TMG) agrees that they are suitable for the trial. This will be decided on a case-by-case basis. Please refer to http://www.addaspirintrial.org/information-for-centres/faqs/ for guidance.
14. Anticipated difficulties in complying with trial treatment or follow-up schedules.
15. <16years old in the UK and Republic of Ireland or <18 years old in India.
16. Participants in other treatment trials where this has not been agreed in advance by both trial teams. A current list of trials where co-enrolment has been approved is available at www.addaspirintrial.org. For further details see section 4.4. For all other trials, this should be discussed with the Trial Managers at the MRC CTU at UCL 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 IV) adenocarcinoma of the colon or rectum* and patients who have undergone resection of liver metastases (at any time) with clear margins and no residual metastatic disease as judged by the multidisciplinary team
2. Patients with synchronous colorectal 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 should be discussed with the MRC CTU at UCL 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 registration and starting run-in treatmentin terms of the treatment pathway should be as described in section 4.2. (For confirmation of standard therapy, please contact MRC CTU at UCL).
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.**
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. A current list of trials where co-enrolment has been approved is available at www.addaspirintrial.org. For further details see section 4.4. If a potential participant is enrolled in a trial that is not listed, this should be discussed with the MRC CTU at UCL or TMC (India) prior to registration.
9. WHO performance status 0, 1 or 2.
10. Written informed consent.

*For patients with colon or rectal cancer who do not have any neoadjuvant treatment, eligibility is based on the histological staging from the resection specimen.
For patients with rectal adenocarcinoma that have neoadjuvant treatment (chemoradiotherapy or radiotherapy alone) eligibility is based on the radiological staging prior to starting neoadjuvant treatment.
** The CaPP3 trial investigating different doses of aspirin to prevent the development of cancer in Lynch syndrome patients has now completed recruitment. Current recommendations (NICE guidelines see attached NICE overview) recommend molecular testing of all colorectal cancers for Lynch syndrome. If the colorectal tumour shows an abnormality of MMR (DNA mismatch repair) protein expression on immunohistochemistry or microsatellite instability, patients should be referred to genetics for counselling and germline testing. If the germline test is not available when the run-in period is due to start potential Add-Aspirin participants can enter the run-in with a review of the result prior to randomisation. If Lynch syndrome is confirmed participants should be referred for a discussion about taking aspirin as cancer chemoprevention.[91]

3.4 COLORECTAL COHORT EXCLUSION CRITERIA

1. Proven (or clinically suspected) metastatic disease (patients who have undergone resection of liver metastases (at any time) 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 I 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*

- *Previous regular use of aspirin ≥5 years ago is acceptable. Any previous regular aspirin use within the last 5 years should be discussed with the MRC CTU at UCL who will advise on eligibility on a case-by-case basis*
- *Current NSAID use is defined as taking any NSAID for more than a week in the preceding month*
- *If investigators feel that these definitions may unfairly exclude a participant, this can be discussed with the MRC CTU at UCL 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 or with a single installation of intravesical chemotherapy or with BCG treatment.
    e. Other cancers where the patient has been disease-free for ≥15 years.
    f. Other cancers with very low potential for recurrence can be discussed with MRC CTU at UCL where eligibility will be considered on an individual basis.
10. Any other condition (physical or psychological) 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, 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 (with no evidence of residual or metastatic disease) unless the participant has been discussed with the MRC CTU at UCL and the TMG agrees that they are suitable for the trial. This will be decided on a case-by-case basis. Please refer to http://www.addaspirintrial.org/information-for-centres/faqs/ for guidance.
14. Anticipated difficulties in complying with trial treatment or follow-up schedules.
15. <16 years old in the UK and Republic of Ireland or <18 years old in India.
16. Participants in other treatment trials where this has not been agreed in advance by both trial teams. A current list of trials where co-enrolment has been approved is available at www.addaspirintrial.org. For further details see section 4.4. For all other trials, this should be discussed with the Trial Managers at the MRC CTU at UCL 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).

See Appendix XIV (section 3B and 3C) for POLEM inclusion/exclusion criteria, for those UK centres involved in screening for the POLEM trial. .

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. Patients will have undergone treatment with curative intent, either: (i) surgery, (ii) radical chemoradiotherapy or (iii) salvage surgery following recurrence after radical chemoradiotherapy.
3. Patients who have undergone surgery with curative intent must have either:
    a. A curative (R0) resection with clear margins (margin ≥1mm or as judged by the multidisciplinary team).
    b. An R1 resection with circumferential margin microscopically positive within 1mm in patients who have undergone an oesophagectomy or oesophagogastrectomy.
4. Patients with M1 nodal disease, where the involved lymph nodes have been encompassed within a radical radiotherapy field, are eligible.
5. Patients who have received standard neo-adjuvant and/or adjuvant treatment or therapy within an agreed trial are eligible. Timing of registration and starting run-in treatment in terms of the treatment pathway should be as described in section 4.2. (For confirmation of standard therapy, please contact MRC CTU at UCL).
6. No clinical or radiological evidence of residual or distant disease according to routine practice staging tests.
7. In the UK and Republic of Ireland: Those who have undergone a gastrectomy or oesophagectomy should be prescribed a proton pump inhibitor for the duration of the trial where no clinical contraindication exists.
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. A current list of trials where co-enrolment has been approved is available at www.addaspirintrial.org. For further details see section 4.4. If a potential participant is enrolled in a trial that is not listed, this should be discussed with the MRC CTU at UCL or TMC (India) prior to registration.
9. WHO performance status 0, 1 or 2.
10. Written informed consent.

3.6 GASTRO-OESOPHAGEAL COHORT EXCLUSION CRITERIA

1. Proven (or clinically suspected) residual or metastatic disease.
2. Patients with stage 1a oesophageal, gastric or gastro-oesophageal junction cancer are not eligible
3. Current or previous regular use of aspirin (at any dose) or current use of another NSAID for any indication (see appendix I 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*
    - *Previous regular use of aspirin ≥5 years ago is acceptable. Any previous regular aspirin use within the last 5 years should be discussed with the MRC CTU at UCL who will advise on eligibility on a case-by-case basis*
    - *Current NSAID use is defined as taking any NSAID for more than a week in the preceding month*
    - *If investigators feel that these definitions may unfairly exclude a participant, this can be discussed with the MRC CTU at UCL and a case by case decision will be made*
4. 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.

5. Current use of anti-coagulants.
6. 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.
7. Active or previous peptic ulceration or gastrointestinal bleeding within the last year, except where the cause of the bleeding has been surgically removed.
8. Active or previous history of inflammatory bowel disease.
9. History of moderate or severe renal impairment, with eGFR<45ml/min/1.73m^2.
10. 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 or with a single installation of intravesical chemotherapy or with BCG treatment.
    e. Other cancers where the patient has been disease-free for ≥15 years.
    f. Other cancers with very low potential for recurrence can be discussed with MRC CTU at UCL where eligibility will be considered on an individual basis.
11. Any other condition (physical or psychological) 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, and patients with a high risk of mortality from another cause within the trial treatment period.
12. Known G6PD deficiency.
13. Known lactose intolerance.
14. LFTs greater than 1.5x the upper limit of normal (with no evidence of residual or metastatic disease) unless the participant has been discussed with the MRC CTU at UCL and the TMG agrees that they are suitable for the trial. This will be decided on a case-by-case basis. Please refer to http://www.addaspirintrial.org/information-for-centres/faqs/ for guidance.
15. Anticipated difficulties in complying with trial treatment or follow-up schedules.
16. <16years old in the UK and Republic of Ireland or <18 years old in India.
17. Participants in other treatment trials where this has not been agreed in advance by both trial teams. A current list of trials where co-enrolment has been approved is available at www.addaspirintrial.org. For further details see section 4.4. For all other trials, this should be discussed with the Trial Managers at the MRC CTU at UCL in the first instance.
18. 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, with clinical or radiological stagingof the prostate T1-3b, N0. See appendix VII 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[92] (prior to radical treatment, see table 3). Also, patients who are low risk prior to prostatectomy but whose prostatectomy histology shows upstaging to pT3b, or a higher Gleason score of 7 or greater are also eligible, including those with microscopic N1 disease provided any additional ADT is not planned for more than 3 years.

Table 3. D'Amico Classification[92]

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	▪ PSAmore 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.
    a. Men treated with immediate adjuvant radiotherapy are eligible. Timing of registration and starting run-in treatment in terms of the treatment pathway should be as described in section 4.2.
    b. In men entering following surgery without adjuvant radiotherapy, PSA at 6-weeks post-surgery should be ≤0.1ng/ml and should remain at this level at the time of entry into the trial, with timing of entry as described in section 4.2. For Indian participants registering before 6 weeks, PSA ≤0.1ng/ml should be confirmed at the time of randomisation.
8. Men receiving neo-adjuvant and/or adjuvant hormone therapy (LHRH agonists, LHRH antagonists, bicalutamide monotherapy) are eligible, provided the planned duration of adjuvant therapy is a maximum of three years. Treatment can be ongoing at the time of registration/randomisation to Add-Aspirin.

(b) Radical radiotherapy patients

9. Men receiving neo-adjuvant and/or adjuvant hormone therapy (LHRH agonists, LHRH antagonists, bicalutamide monotherapy) are eligible provided the planned duration of

adjuvant therapy is a maximum of three years.tThis treatment may be ongoing at the time of registration in Add-Aspirin.

10. Timing of registration and starting run-in treatment 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)

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

3.8 PROSTATE COHORT EXCLUSION CRITERIA

1. Biopsy proven or radiologically suspected nodal involvement or distant metastases from prostate cancer.
    a. T4 patients are ineligible.
2. Adjuvant hormone therapy planned for >3years.
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 I 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*
    - *Previous regular use of aspirin ≥5 years ago is acceptable. Any previous regular aspirin use within the last 5 years should be discussed with the MRC CTU at UCL who will advise on eligibility on a case-by-case basis*
    - *Current NSAID use is defined as taking any NSAID for more than a week in the preceding month.*
    - *If investigators feel that these definitions may unfairly exclude a participant, this can be discussed with the MRC CTU at UCL 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 within the last year, 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 or with a single installation of intravesical chemotherapy or with BCG treatment.
    d. Other cancers where the patient has been disease-free for ≥15 years.

e. Other cancers with very low potential for recurrence can be discussed with MRC CTU at UCL where eligibility will be considered on an individual basis.

12. Any other condition (physical or psychological) 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, 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 (with no evidence of residual or metastatic disease) unless the participant has been discussed with the MRC CTU at UCL and the TMG agrees that they are suitable for the trial. This will be decided on a case-by-case basis. Please refer to http://www.addaspirintrial.org/information-for-centres/faqs/ for guidance.
16. Anticipated difficulties in complying with trial treatment or follow-up schedules.
17. <16years old in the UK and Republic of Ireland or <18 years old in India.
18. Participants in other treatment trials where this has not been agreed in advance by both trial teams. A current list of trials where co-enrolment has been approved is available at www.addaspirintrial.org. For further details see section 4.4. For all other trials, this should be discussed with the Trial Managers at the MRC CTU at UCL or TMC (India) prior to registration.

3.9 NUMBER OF PARTICIPANTS

The target randomisation figure is 9,920 participants (across all countries). 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 is normally expected to be no more than 1 month prior to registration and should be done once the participant has had adequate time to read the Participant Information Sheet (PIS) (see Participant Information Sheet). Informed consent should be taken after explanation of the aims, methods, potential benefits and hazards of the trial and **before** any trial-specific procedures are performed and blood samples are taken for the trial or any trial tablets are dispensed (see Consent Form). This can be carried out by the Investigator or by a Research Nurse in the UK. 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. A Participant Introductory Leaflet can be provided to the participant early on in their treatment pathway to make them aware of the trial, prior to giving them the PIS (see Participant Leaflet) – please note that this is not mandatory.

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 and a copy given to the participant; in the UK a copy should be sent to the MRC CTU at UCL and 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) 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. For colorectal participants in the Add-Aspirin – POLEM Collaboration, please follow the separate Trial Assessment Schedule found in Appendix XIV.

4 REGISTRATION AND RANDOMISATION

UK, INDIA & REPUBLIC OF IRELAND - REGISTER PARTICIPANTS ONLINE AT:
www.addaspirintrial.org

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

INDIA & REPUBLIC OF IRELAND - RANDOMISE PARTICIPANTS ONLINE:
www.addaspirintrial.org

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

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.

For those who do not go on to be randomised, active participation in the trial will end at this time and no further CRFs are required after the end of run-in assessment. However, passive follow-up will continue via routinely-collected healthcare datasets, if the participant has 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 section describes when the active run-in period can be started relative to the treatment pathway. Potential participants can be given information about the trial before this time. 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, or cases where potential participants fall outside of the timing of entry criteria, and there is a valid reason, please discuss with the MRC CTU at UCL where eligibility will be considered on a case by case basis. In all cases, timing of entry into the run-in period is calculated from the most recent curative treatment received.

4.2.1 BREAST COHORT

For these participants, hormone therapy and/or trastuzumab may be planned or ongoing. A diagram of the timing of entry criteria for the breast cohort is available in appendix VIII.

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 ended (e.g. day 21 of a 3 week cycle) and no later than 6 weeks after the end of 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 ended (e.g. day 21 of a 3 week cycle) and no later than 6 weeks after the final fraction of radiotherapy.

4.2.2 COLORECTAL COHORT

A diagram of the timing of entry criteria for the colorectal cohort is available in appendix IX.

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. **India only:** the run-in period should start between 2 and 12 weeks after definitive surgery.

b) **Surgery and adjuvant chemotherapy (no radiotherapy planned):** the run-in period can start after 6 weeks of ongoing chemotherapy providing that the platelet count on day 1 of each of the preceding chemotherapy cycles is $\geq 100 \times 10^9$/L. The run-in period should start no later than 6 weeks after the end of chemotherapy including when chemotherapy has been discontinued early (e.g. day 14 of a 2 week cycle or day 21 of a 3 week cycle). There is no minimal amount of 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.

e) ***Surgery and entry into POLEM trial - if randomised to adjuvant chemotherapy and Avelumab** (24 week treatment): the run-in period can start after completion of Avelumab and no later than 6 weeks after the end of avelumab.

f) ***Surgery and entry into POLEM trial – if randomised to adjuvant chemotherapy alone (control arm):** the run-in period can start after completion of chemotherapy and no later than 6 weeks after the end of chemotherapy.

*See Appendix XIV for further details regarding Add-Aspirin – POLEM Colorectal Collaboration in selected centres.

4.2.3 GASTRO-OESOPHAGEAL COHORT

A diagram of the timing of entry criteria for the gastro-oesophageal cohort is available in appendix X.

a) **Surgery and no adjuvant chemotherapy or radiotherapy planned (but may have been preceded by chemotherapy):** In the UK and Republic of Ireland, the run-in period should start between 6 and 16 weeks after definitive surgery. **India only:** the run-in period should start between 2 and 16 weeks after definitive surgery.

b) **Surgery and adjuvant chemotherapy:** the run-in period can start after 6 weeks of ongoing chemotherapy providing that the platelet count on day 1 of each of the preceding chemotherapy cycles is $\geq 100 \times 10^9$/L. The run-in period should start no later than 8 weeks after the end of chemotherapy (day 21 of a 3 week cycle) including when chemotherapy has been discontinued early. There is no minimal amount of chemotherapy.

c) **Surgery and adjuvant chemoradiotherapy:** the run-in period can start after 6 weeks of chemoradiotherapy providing platelet counts as defined in (b) above. The run-in period should start no later than 14 weeks after the last fraction of radiotherapy.

d) **Definitive chemoradiation:** the run-in period can start as soon as this is complete and no later than 14 weeks after the final fraction of radiotherapy. Where a post-treatment endoscopy is routinely performed at 12 weeks after chemoradiotherapy, the run-in period can start once this has been undertaken and up to four weeks after.

e) **Definitive chemoradiation followed by salvage surgery:** In the UK and Republic of Ireland, the run-in period should start between 6 and 16 weeks after definitive surgery. India only: the run-in period should start between 2 and 16 weeks after definitive surgery.

4.2.4 PROSTATE COHORT

For these participants, hormone therapy may be planned or ongoing (for a maximum duration of 3 years). A diagram of the timing of entry criteria for the prostate cohort is available in appendix XI.

a) **Prostatectomy and no adjuvant chemotherapy or radiotherapy planned:** the run-in period should start between 6 and 12 weeks after definitive surgery, providing PSA remains ≤0.1 ng/ml at point of entry. **India only:** the run-in period should start between 2 and 12 weeks after definitive surgery and – where registration is before 6 weeks - PSA ≤0.1ng/ml should be confirmed at the time of randomisation.

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.

If there are any problems for centres accessing the system, the Trial Managers at the MRC CTU at UCL 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 a number of specified trials may enter Add-Aspirin (providing they satisfy all other eligibility criteria). This has been agreed with the relevant trial teams. For the most up-to-date list, check www.addaspirintrial.org. If they have participated in another trial that is not listed on the approved list, please contact the MRC CTU at UCL to discuss this prior to their registration into Add-Aspirin. Following registration, participation in another trial should be reported on the Co-enrolment CRF. Note that participation in a previous observational study (where the patient has received treatment as per standard of care) does not require prior approval or reporting on CRFs.

Following entry into Add-Aspirin, if participants should wish to enter subsequent cancer treatment trials (particularly where this is prior to an Add-Aspirin primary outcome event), please contact the Trial Manager to discuss this.

If you have any queries regarding co-enrolment, please contact the MRC CTU at UCL.

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 (7-9 weeks is acceptable) 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. 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 significant gastrointestinal bleeding (grade 3 and 4), active gastrointestinal ulceration, new cases or worsening tinnitus (grade 2 or above), , 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 and the blinded medication should be commenced as close to the end of the run-in period as possible.

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, and at a similar time each day. 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 automatically only be randomised to aspirin 100mg or matching placebo. Additionally, prescription of a proton pump inhibitor (PPI) throughout the treatment period is recommended for these patients.

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 to the centre pharmacist in the Drug Supply Management System (DSMS) user guide.

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 and should be dispensed via DSMS (including open-label run-in packs).

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 II) 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. See section 5.6.1 for further information on unblinding. 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. nosebleeds, 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 can occur with concurrent use of sulphonylurea antidiabetic medication.
- Hyperuricaemia - 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.

It has been suggested that aspirin could be linked to an eye condition called age-related macular degeneration (age-related loss of sight), however evidence has been conflicting and this has not been confirmed.

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 II).

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 https://www.nice.org.uk/guidance/CG184[93] 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, in the UK and Republic of Ireland, PPI use for the duration of aspirin treatment is mandated for patients who have undergone oesophagectomy or gastrectomy and is also recommended for elderly patients (≥75 years), or any other participant who might be at increased risk of toxicity. In India, PPI use is as per local practice.

Intracranial bleeding is a rare toxicity of aspirin. Hypertension can increase the risk of an intracranial bleed. All participants should have blood pressure assessed prior to registration and throughout participation in the trial, in accordance with the assessment schedules. For information on the management of hypertension please refer to section 5.4.3.C.

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 knowledge of treatment allocation would alter management (see section 5.6).

5.4.2.A Prophylactic Use of Histamine Receptor Antagonists

Where an investigator feels it is clinically appropriate to use a histamine receptor antagonist in place of a proton pump inhibitor for patients at high risk of gastro-intestinal toxicity, or for the treatment of gastro-intestinal toxicity, this will be acceptable within Add-Aspirin. In patients who have undergone a gastrectomy or oesophagectomy in the UK and Republic of Ireland, a proton pump inhibitor should be used, however a histamine receptor antagonist would be an acceptable alternative where a proton pump inhibitor is contraindicated.

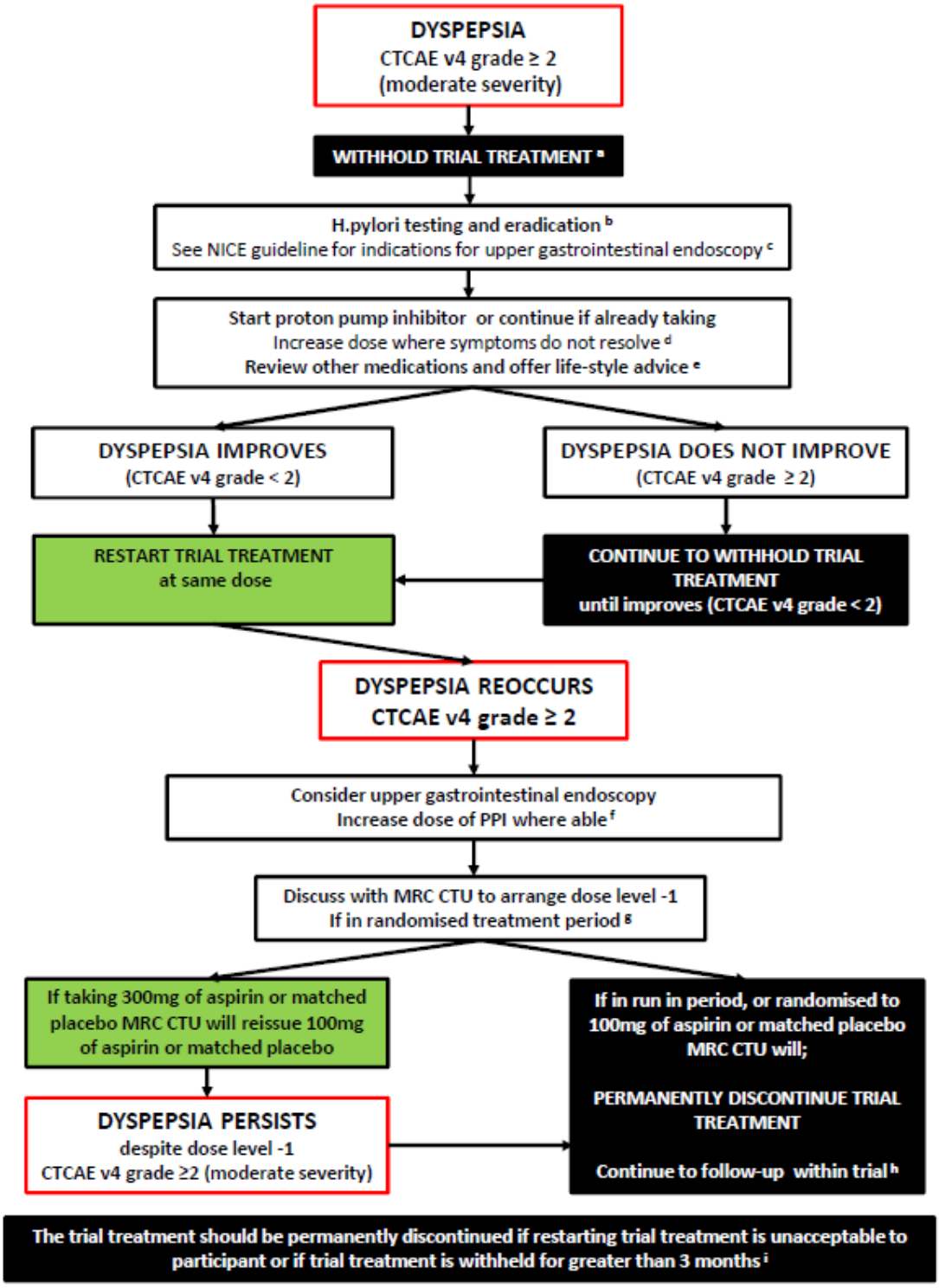
5.4.3 TOXICITY MANAGEMENT

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 gastrointestinal bleeding (immediate referral if significant acute bleeding), progressive dysphagia, iron deficiency anaemia or persistent vomiting.[94]

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.[93]

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 should be recorded in the relevant section on the Follow-Up CRF (Form 8).

b. All participants with grade ≥ 2 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[93]. 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.[93]
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[93]).
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.[95]
g. Those on the higher dose of trial treatment can have their dose reduced (dose level-1). MRC CTU at UCL 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 period 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 significant gastrointestinal bleeding (grade 3 or 4) whilst taking the trial medication it should be permanently discontinued. Where significant gastrointestinal bleeding (grade 3 or 4) occurs in the trial run-in period, 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.

For less significant episodes of gastrointestinal bleeding (grade 1 or 2) – particularly if the cause is not directly related to aspirin/trial medication, clinical discretion should be applied as to whether trial treatment should be discontinued. Individual cases can be discussed with clinical members of the trial management group by contacting the MRC CTU at UCL. Trial medication can be withheld (for up to 3 months) while clinical investigations/decisions are considered.

5.4.3.C Management of Other Toxicities

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

- Gastrointestinal bleeding (grade 3 or 4)(see section 5.4.3.B)
- Active gastrointestinal ulceration
- New or worsening tinnitus or hearing loss (grade 2 or above)
- Intracranial bleeding
- Hypersensitivity to aspirin
- Other toxicities can be discussed with MRC CTU at UCL

OTHER TOXICITY

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 at UCL 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.
  Wherever the trial treatment has been permanently discontinued, follow-up in the trial should continue. Participants who discontinue during the run-in period will be asked for consent to allow passive follow-up data collection using medical records, however no further CRFs will be completed

TINNITUS

For new episodes of tinnitus of grade 1, aspirin/trial medication can be discontinued for up to 3 months to see if symptoms change or resolve when the trial medication is not being administered, before a definitive decision is made regarding permanent discontinuation of trial medication. Individual cases can be discussed with clinical members of the trial management group by contacting the MRC CTU at UCL.

HYPERTENSION

All participants should have blood pressure assessed prior to registration and throughout participation in the trial, in accordance with the assessment schedules (see flexibility of schedule and follow-up for further information). Patients with a systolic BP≥160mmHg or diastolic BP ≥100mmHg (confirmed on repeated measurement, home monitoring or ambulatory monitoring) prior to registration should have blood pressure treatment optimised before registration.

Patients who are already registered in the trial who have hypertension (BP≥160mmHg or diastolic BP ≥100mmHg), confirmed on repeated measurement, should be referred to their GP for a repeat measurement and blood pressure optimisation where required, or a repeat reading should be taken at home.

If the blood pressure remains elevated (systolic BP≥160mmHg or diastolic BP ≥100mmHg) on repeated measurement, either at the GP or at home, then please withhold treatment (up to 3

months) until BP is optimised, and notify MRC CTU. An in range reading must be obtained prior to the patient recommencing trial treatment.

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

eGFR
If a participant's eGFR falls below 45ml/min/1.73m^2, please investigate other causes of a deterioration in renal function and consider withholding trial medication until this level improves. Discuss with the MRC CTU for advice.

See Appendix XIV for management of immune related toxicity in POLEM

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.[95] 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, trial treatment should be stopped and a Pregnancy CRF (Form 14) and SAE/Notable Event CRF (Form 11) should be completed; this should also be discussed directly with the Trial Manager. Please refer to section 7.2 for further information. 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. The MRC CTU at UCL 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). In the UK, for additional guidance please contact the National Poisons Information Service (www.toxbase.org).

5.6 UNBLINDING

Randomisation codes are held within the MRC CTU at UCL 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 knowledge of treatment allocation 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.

Unblinding for any purpose other than a medical emergency is generally not allowed, but individual cases should be discussed with the MRC CTU at UCL or TMC/CRO 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 (Form 13). 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 at UCL, TMC, CRO) will remain blinded.

5.6.1.A UK Unblinding

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 at UCL by contacting the Add-Aspirin Trial Managers who will contact one of the Trial Physicians. During 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 be performed via an access-controlled system available through the trial website (**www.addaspirintrial.org**).

5.6.1.B India Unblinding

: Where unblinding is being considered, the CRO should be contacted in the first instance. The case will normally then be referred to the clinical leads at TMC for advice before unblinding is performed. Full details of this process, including contact details are provided in the Indian group specific appendix.

5.6.1.C Republic of Ireland Unblinding

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 at UCL by contacting the Add-Aspirin Trial Managers who will contact one of the Trial Physicians. During out of hours, the Principal Investigator and other authorised invesitgators are able to access the unblinding system.

The PI or investigator 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 be performed via an access-controlled system available through the trial website (**www.addaspirintrial.org**).

For further unblinding information, please refer to the Add-Aspirin Unblinding Procedure For Site – Republic of Ireland.

5.6.2 UNBLINDING FOR SAFETY REPORTING

MRC CTU at UCL 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 (Form 12).

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 6.9.

5.8 TREATMENT FOLLOWING DISEASE RECURRENCE/PROGRESSION

When disease recurrence has occurred in patients during the randomised phase of the study, 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 at UCL.

If a disease recurrence event happens during the run-in phase, the participant will not be eligible for randomisation and should not be followed up in the trial.

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 DSMS user guide and Add-Aspirin Pharmacy Working Instructions.

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 I 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 I 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. If longer term use of non-permitted medication is necessary, a treatment break should be initiated. If use is to be longer than 3 months trial treatment should be permanently discontinued. If a patient is found to have been using non-permitted medication concomitantly with trial medication, clinical review of the patient should be performed and MRC CTU should be contacted for advice.

5.11.3 MEDICATIONS TO BE USED WITH CAUTION

Aspirin has the potential to interact with the following medications and should therefore be taken with caution: 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.

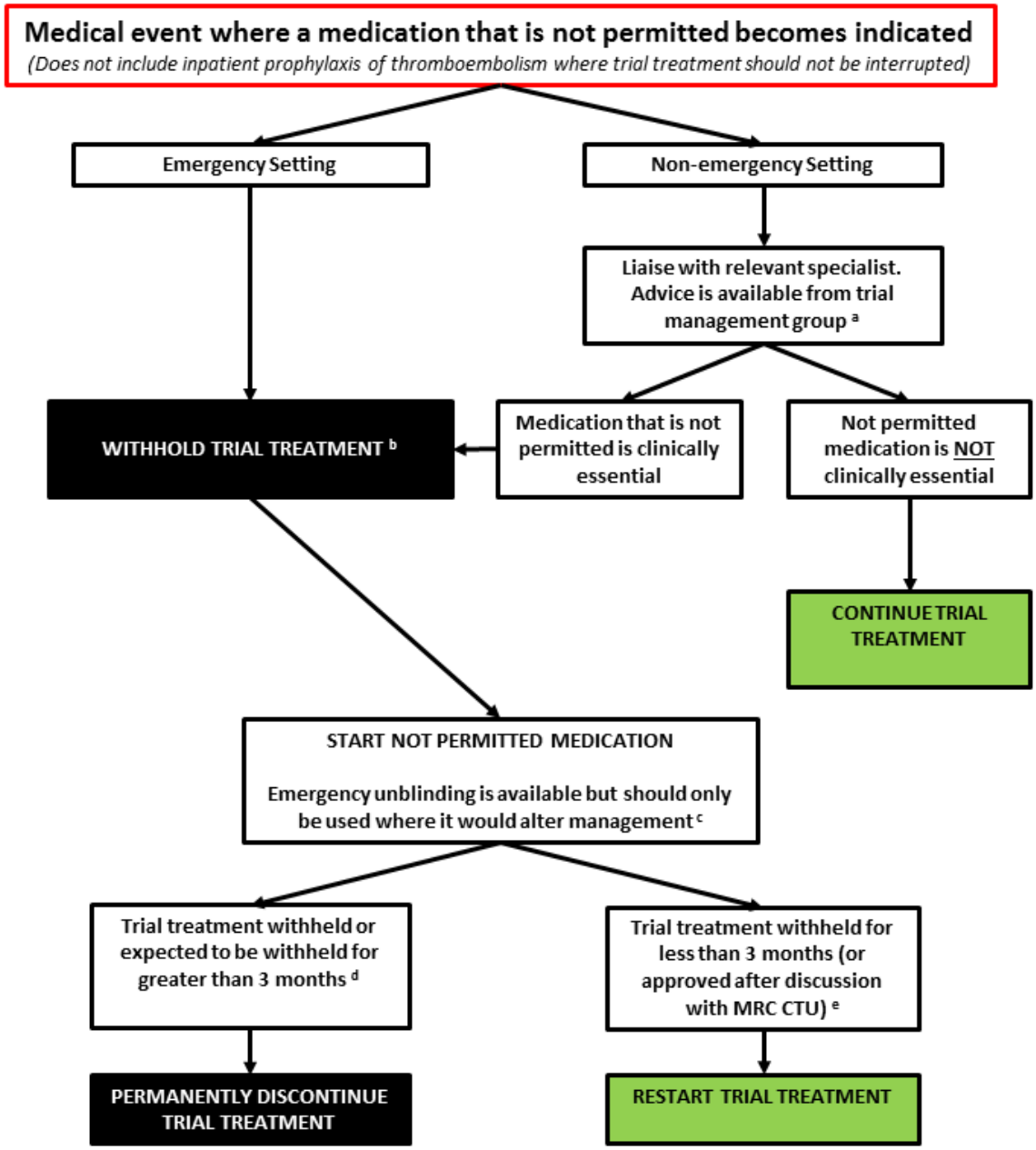
5.11.4 MANAGEMENT WHERE A MEDICATION THAT IS NOT PERMITTED BECOMES INDICATED DURING THE TRIAL

We would not expect patients who require a medication that is not permitted in the trial (see appendix I) 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 (figure 3) 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 period 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, provided it has been withheld for less than 3 months (if greater than 3 months, individual cases can be discussed with MRC CTU at UCL).

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 at UCL should be informed of any event where a medication that is not permitted becomes indicated. If applicable the appropriate SAE and Notable Event CRF (Form 11) 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 adherence 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.

The run-in period should be 7-9 weeks long. 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 significant gastrointestinal bleeding (grade 3 or 4), active gastrointestinal ulceration, new cases or worsening tinnitus (grade 2 or above), 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). Additionally this may apply to patients who may be eligible for CAPP3 and are awaiting results of genetic testing. 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 at UCL via the Trial Managers and only one extension for a maximum of 8 weeks is permitted per participant.

6.3 PROCEDURES FOR ASSESSING EFFICACY

Clinical outcome events, as defined in the Statistical Analysis Plan, will be reported on 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). In the prostate cohort, biochemical failure is a primary outcome event and should be reported in accordance with the definitions provided in 6.3.1.

Following disease recurrence/progression in the randomisation phase, 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.

6.3.1 DEFINITIONS OF BIOCHEMICAL FAILURE EVENTS IN THE PROSTATE COHORT

In the prostate cohort, biochemical (PSA) failure is a primary outcome event and is defined as follows, according to primary treatment pathway:

- **Participants who have undergone prostatectomy:** failure occurs in the case of a PSA value greater than 0.2ng/ml, observed at least 6 weeks after surgery, which is confirmed by a subsequent PSA value higher than the first[a].
- **Participants who have undergone radical radiotherapy:** the failure value is defined as nadir+2ng/ml[b], with failure occurring in the case of a PSA value exceeding the failure value which is confirmed by a subsequent PSA value higher than the first[a].
- **Participants who have undergone salvage radiotherapy (following a rise in PSA after prostatectomy)**: failure occurs in the case of:
    - (i) a PSA value greater than 0.1ng/ml which is confirmed by a subsequent PSA value higher than the first[a]; or
    - (ii) three consecutive rising PSA values

Notes on the definitions:

a) In all cases the confirmation PSA test should be performed between 1 week and 3 months after the initial failure. The event will be reported as having occurred on the date of the original (first) test with the corresponding PSA value.
b) The PSA nadir will be the lowest reported PSA value between registration and (up to and including) the 6-month follow-up visit.

6.4 PROCEDURES FOR ASSESSING SAFETY, ADHERENCE AND OTHER TRIAL EVENTS

Aspirin 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 Non-Cancer Event CRFs (Form 10).
Where a trial visit is additional to local standard care, assessments can be conducted via telephone follow-up providing that all the required information can be obtained, and appropriate measures for dispensing trial medications are made. 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.[96] 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) FOR UK AND REPUBLIC OF IRELAND ONLY

Functional capacity will be assessed using the VES-13.[97] 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 (Functional Status CRF (Form 5)) 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.

The VES-13 will not be performed in India due to the lack of validated translations; this will not affect the safety of the patients nor the required efficacy assessments.

6.7 COGNITIVE ASSESSMENT USING THE MOCA-BLIND FOR UK AND REPUBLIC OF IRELAND ONLY

The hypothesis that aspirin protects against cognitive decline will be assessed using a short version of the Montreal Cognitive Assessment (the MoCA-blind). This short questionnaire (Cognitive Assessment CRF (Form 6)) tests cognitive functioning across five domains: attention, language, abstraction, memory recall and orientation. The MoCA-blind 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. No formal training is required to administer the questionnaire – instructions are included as part of the CRF (and an audio recording of the questionnaire being administered is available on the website, addaspirintrial.org). It can be administered by a non-clinical member of staff (for example, a Data Manager), providing that delegation of the task is appropriately documented on the delegation log. The questionnaire can also be administered over the phone where no clinic visit is planned.

The cognitive assessment will not be performed in India due to the lack of validated translations; this will not affect the safety of the patients nor the required efficacy assessments.

6.8 EXERCISE QUESTIONNAIRE

The measurement of physical activity levels in Add-Aspirin participants across 4 tumour sites will investigate the association between physical activity and cancer and non-cancer outcomes. The International Physicial Activity Questionnaire (IPAQ) takes approximately five minutes and will be administered in all Add-Aspirin participants at one and five years after randomisation. It is included in the Follow Up CRF (Form 8) and can be administered by a non-clinical member of staff (for example, a Data Manager) as part of the follow up visit or can be self-administered by the

participant. To address cultural differences, the examples of exercise given in the IPAQ have been modified to suit Indian participants' understanding of exercise efforts.

6.9 EARLY STOPPING OF FOLLOW-UP

If trial treatment is discontinued, for whatever reason, this should be documented on the relevant CRF. During the run-in this should be recorded on the End of Run-in CRF (Form 7). During the randomised phase this should be recorded on an Early Cessation of Trial Treatment CRF (Form 12). If discontinuation during the randomised phase is caused by an aspirin related toxicity, a Notable Event CRF (Form 11) should be submitted. Following discontinuation of trial treatment 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, their decision must be respected and the participant will be withdrawn from the trial completely. The MRC CTU at UCL 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 at UCL 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 at UCL 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 order to collect long-term follow-up data in India and Republic of Ireland, participants will be contacted on an annual basis for a further 5 years.
In all 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. For further information relating to withdrawal please refer to the Withdrawal Guidance Document.

6.10 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 UCL at the earliest opportunity. A patient transfer form should be completed by both the old and new site to confirm the transfer. 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.

Where centres are participating in screening for the POLEM trial, but are not participating fully in that trial, patients will normally transfer to a nearby POLEM centre to receive POLEM treatment and will subsequently transfer back to the original Add-Aspirin centre for recruitment into Add-Aspirin if relevant. Please see Appendix XIV for details.

6.11 TRIAL CLOSURE

The trial will be considered closed approximately 10 years after the last participant was randomised, when all participants have completed follow-up in the trial.

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 IMPs, 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

The following events, in the context of this trial, do not require reporting on Serious Adverse Event (SAE) forms.

- Medical or surgical procedures; the condition that leads to the procedure is the adverse event
- 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 as a Notable Event on an SAE and Notable Event CRF (Form 11) and sent to the MRC CTU at UCL (in the UK) or the CRO (in India) 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 (Form 14). 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 at UCL (in the UK) or the CRO (in India) if there is any suspicion of any adverse effect of the trial medication.

7.2.2 EARLY CESSATION

Any early cessations of Add-Aspirin trial treatment due to toxicity or adverse event should be reported as a Notable Event on an SAE and Notable CRF (Form 11). Forms should be sent to the MRC CTU at UCL (in the UK and Republic of Ireland) or the CRO (in India) via fax or galaxkey within 24 hours of the Investigator being aware of the event.

The clinical team responsible will be asked to inform the MRC CTU at UCL (in the UK and Republic of Ireland) or the CRO (in India) if there is any suspicion of any adverse effect of the trial medication.

7.3 INVESTIGATOR RESPONSIBILITIES

All non-serious ARs, whether expected or not, should be recorded in the participant's medical notes. Only aspirin related ARs should be reported in the toxicity section of the Follow-Up CRF (Form 8) at the next visit. The form should then be sent within one month to the MRC CTU at UCL (for UK and Irish participants) or entered on to the trial database (for India participants).

The MRC CTU at UCL (for UK and Irish participants) or CRO (for Indian participants) 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 recurrence, progression or another event exempted from expedited reporting (see section 7.1.3)**, then an SAE and Notable Event Form must be completed and the MRC CTU at UCL (UK and Republic of Ireland) or the CRO (India) 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 grading in appendix II (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 II for a list of common 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 at UCL (for UK and Irish participants) or the CRO (for India participants) should be notified of all SAEs within 24 hours of the Investigator at site becoming aware of the event. This is with the exception of events relating to recurrence/progression of the patient's primary cancer (including death due to primary cancer), or a diagnosis of a new cancer, which are required to be reported on SAE forms, but can be submitted within the normal timelines for CRF return (ie. within 1 month of the event).

In India, SAE reporting should follow local regulations and Ethics Committee SOPs. Upon receipt, the CRO should notify the MRC CTU at UCL of all SAEs within 1 working day.

Investigators should notify the MRC CTU at UCL (UK and Republic of Ireland) or the CRO (India) of all SAEs occurring from the time the participant starts taking the trial medication (including the run-in period) until 30 days after the last protocol treatment administration. SARs and SUSARs must be notified to the MRC CTU at UCL or the CRO in India until trial closure.

7.3.2 NOTIFICATION PROCEDURE

1. The SAE and Notable Event 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 to the trial team at MRC CTU at UCL (UK and Republic of Ireland) or the CRO (India). The responsible Investigator should subsequently check the SAE and Notable Event Form, make changes as appropriate, sign and then re-fax to the MRC CTU at UCL or the CRO 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, SAE name, name of Investigator reporting and an indication of why the event is considered serious.

2. The SAE and Notable Event Form must be sent to the MRC CTU at UCL (UK and Irish sites) or CRO in India. Receipt will be confirmed.
   The event must be sent to MRC CTU at UCL Fax: +44 (0)20 7670 4818 or via Galaxkey to: mrcctu.add-aspirin@ucl.ac.uk
3. Galaxkey should be used where fax is no longer available. Please contact the Trial Managers at MRC CTU at UCL if you require access to Galaxkey.
   CRO Fax: +91 129 6613510; email: safety@jssresearch.com
   The CRO will onward report SAEs and SARs to TMC and MRC CTU at UCL within 24 hours of receipt.

4. 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 and Notable Event Form(s), indicated as 'Follow-up' should be completed and faxed to the MRC CTU at UCL (UK and Irish patients) or CRO in India 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.

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

UK and Republic of Ireland- SAE REPORTING
Within 24 hours of becoming aware of an SAE, please send a completed SAE and Notable Event Form to the MRC CTU at UCL by fax:
Fax: 020 7670 4818
or send via galaxkey to the trial mailbox:
Galaxkey: mrcctu.add-aspirin@ucl.ac.uk

INDIA - SAE REPORTING
Within 24 hours of becoming aware of an SAE, please send a completed SAE and Notable Event Form to the CRO:
Fax: +91 129 6613510
Email: safety@jssresearch.com

7.4 SPONSOR 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 at UCL is undertaking the duties of trial sponsor and is responsible for the reporting of SUSARs and other SARs to the regulatory authorities and research ethics committees in the UK, as appropriate. Fatal and life-threatening SUSARs must be reported to the Competent Authorities (Regulatory Authority and Ethics Committees) within 7 days after the MRC CTU at UCL becomes aware of the event; other SUSARs must be reported within 15 days. Expedited reporting and report submission in India will be the responsibility of TMC, the co-sponsor in India, or the CRO as its delegate. MRC CTU at UCL will forward all Irish SUSARs as required to Cancer Trials Ireland for

onward reporting. Cancer Trials Ireland will be responsible for reporting SUSARs in the Republic of Ireland to the Irish regulatory body and EMA via EudraVigilance as well as the Irish Central Ethics Committee.

The MRC CTU at UCL will submit Annual Safety Reports in the required format to UK Competent Authorities (Regulatory Authority and Ethics Committee). Submission of Annual Safety Reports to Indian authorities and ethics committees will be performed by the TMC or the CRO as its delegate.

The MRC CTU at UCL 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 and SARs. MRC CTU at UCL will also provide Bayer Pharmaceuticals and CIPLA Ltd 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 at UCL Research Governance Committee (RGC).

8.2 CENTRAL MONITORING AT MRC CTU AT UCL

MRC CTU at UCL 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 the Add-Aspirin Monitoring Plan. This plan will also detail the procedures for review and sign-off. To responsibility of on-site monitoring in the Republic of Ireland has been delegated to Cancer Trials Ireland.

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. Participants' 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 (AT SELECTED UK CENTRES)

Urinary excretion of 11-dehydro-thromboxane B_2 (TXM) (a major enzymatic metabolite of thromboxane A2/thromboxane B2) provides an indication of in vivo platelet activation, and its use has been demonstrated in the evaluation of the role of platelet activation in atherothrombosis.[98] Persistent platelet activation as reflected by enhanced excretion of TXM, 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.[99] 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.[19] 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 TXM excretion has 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[100], as well as providing a measurement of adherence. Although platelet activation has been implicated in the development and spread of colorectal cancer, there have been no studies to date on patients with other cancers.

Urinary excretion of TXM will be measured in 500 patients (from selected UK centres): 150 patients from each of the breast, colorectal and prostate cohorts and 50 gastro-oesophageal patients) at baseline, at the end of the 8 week run-in period and after 3 months of randomised treatment (placebo, aspirin 100mg or 300 mg daily). Platelet activation will be assessed at baseline across the 4 tumour-specific disease states and in relation to traditional cardiovascular risk factors. The effect of aspirin (100 mg daily during the run-in period) in reducing urinary TXM excretion will be compared across the 4 tumour cohorts, and in relation to body mass index (BMI) and/or diabetes mellitus. The subsequent effect of the randomised intervention (aspirin 100mg, aspirin 300mg or placebo daily) will be assessed after 3 months.

Patients will be asked to provide consent for this translational study at the time of trial registration, but may choose not to participate, and this will not affect their participation in the main trial. Participants who provide consent will be asked to donate three samples of urine at the timepoints indicated above. At each timepoint, participants will provide a 6ml urine sample in a sterile container to be posted, without any onsite processing, to one of the biobanks. The same Royal Mail safe box used for blood samples should be used at registration where possible.

In a subset of these patients (recruited at selected centres) whole blood samples will be collected at the same time points, at the end of the 24-hour dosing interval (i.e, immediately before the next aspirin administration), and allowed to clot at 37° C for 60 min for the blinded measurement of serum TXB2, a highly specific index of platelet COX-1 activity, to monitor the extent of compliance with the experimental treatment, assessthe rate of consumption of COX-1 inhibitors in the placebo arm and to validate the results of the urine substudy.

9.2 SAMPLE COLLECTION FOR FUTURE TRANSLATIONAL RESEARCH

The Add-Aspirin bio-bank 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 is 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 a formalin fixed paraffin embedded (FFPE) tumour sample and a blood sample at baseline (with the exception that, in India, only TMC is participating in the blood sample collection). Participants will be asked to provide consent for sample collection at the time of registration but may choose not to participate in 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 provided packaging to one of the two UK repositories. Further information on the process is provided in the Translational Manual. If the sample is missed for a patient who has provided consent please contact the MRC CTU for guidance.

In India, one 10ml whole blood sample will be collected and stored for consenting patients at TMC only. An FFPE tumour sample will be collected for consenting patients at all Indian sites and will be sent to TMC to be stored.

In Ireland, one 10ml whole blood sample will be collected prior to any aspirin administration for consenting patients, the sample will then be processed and stored locally at Irish sites until arrangements are made for transfer to the UK biobank. For full details on the sample collection process please refer to the Add-Aspirin Ireland Specific Translational Manual.

In a subset of colorectal participants who have undergone treatment within the POLEM trial, additional research blood samples will be required at each POLEM visit (see Appendix XIV for more details).

Further Add-Aspirin sample collections may be initied while the trial is ongoing subject to funding and obtaining the approiate approvals and consent..

9.2.2 PIK3CA MUTATIONS

The potential importance of PIK3CA mutations to predict response to aspirin, particularly in colorectal cancer, has been identified.[25,27] Subject to funding, samples from participants in this cohort (who have provided the appropriate consent) will be used to test for the PIK3CA mutation during the run-in period. 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 national registries and 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 hospital episode data); 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 for those participants who give consent. These data will be stored separately to the main trial database.

A period of overlap between active trial follow-up and this 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, and potentially also 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 THE IMPACT OF PARTICIPANT NEWSLETTERS (UK CENTRES ONLY)

Participant engagement and retention is an important aspect of the trial, since participants are being asked to self-medicate daily for a period of at least 5 years, and patient representatives on the Trial Management Group have highlighted increased communication with participants (from the central trial team) as a method which might help to improve/maintain engagement over the course of the trial. In order to assess this, newsletters for participants will be piloted for a period of approximately 2 years, and will be distribed via research staff at all recruiting UK centres, with the option for participants to subscribe to an electronic mailing list. After the pilot period, particpants will be asked to complete a short, one-off questionnaire aimed at evaluating the impact of the newsletters in terms of participant engagement and the likelihood of an impact on adherence to trial medication

and follow-up schedules. Views from research staff at participating centres will also be elicited. Dependent on the feedback, the newsletters may be continued beyond the initial pilot period.

9.3.3 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, and the conduct of the run-in period will be evaluated.

9.4 STUDIES ASSESSING LIFESTYLE AND QUALITY OF LIFE IN PEOPLE LIVING WITH AND BEYOND CANCER

With more and more people surviving longer following a cancer diagnosis and treatment, a better understanding of the long-term impact on health and quality of life, and how this is influenced by lifestyle choices, is currently a key research priority. To this end, the Add-Aspirin trial incorporates studies which will assess these aspects within the four tumour-specific cohorts, with the aim of informing future research:

- A questionnaire assessing exercise levels over time in the trial cohorts will be used to investigate the association between exercise and both cancer and non-cancer outcomes, with the potential to inform future lifestyle intervention strategies.
- A further study assessing the long-term impacts of cancer diagnosis and treatment on health and quality of life life is also being developed, and will be added later in the trial via a protocol amendment. This study may help to identify priorities and direct future research in these cohorts.

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 table7. Details of outcome assessments are given in section 6.

Table 7: Primary outcome measures

COHORT	PRIMARY OUTCOME MEASURE
Cohorts combined	**Overall survival (OS)** Time from randomisation to death from any cause
Breast cancer	**Invasive disease-free survival (IDFS)** Time from randomisation to invasive disease or death from any cause. Invasive disease is defined as: • Ipsilateral invasive breast tumour recurrence • Regional invasive breast cancer (ipsilateral breast) • Distant recurrence • Contralateral invasive breast cancer • Second primary (non-breast) invasive cancer
Colorectal cancer	**Disease-free survival (DFS)** Time from randomisation to disease recurrence (local or distant) or death from any cause.
Gastro-oesophageal cancer	**Overall survival** Time from randomisation death from any cause.
Prostate cancer	**Biochemical recurrence-free survival (bRFS)** Time from randomisation to PSA failure (as defined in 6.3.1), clinical progression, initiation of salvage treatment or prostate cancer death.

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. 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 is also a translational sub-study which will assess adherence based on thromboxane B_2 levels measured in urine and 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)[101]

COHORT	SECONDARY OUTCOME MEASURE
	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-Blind)
	Dementia Diagnosis of dementia (of any type), reported by sub-type
	Functional capacity Using the VES-13 questionnaire
	Exercise levels Measured using the International Physical Activity Questionnaire (IPAQ)
	Long-term quality of life/late effects of cancer treatment Measured using survivorship 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[102]
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

10.3.1 COHORT-SPECIFIC ANALYSES OF PRIMARY OUTCOME DATA

The cohort-specific primary outcomes are all time-to-event variables with events as defined above. Participants that have not yet experienced the event in question at the time of analysis will be censored on the date they were last known to be event-free.

At the time the trial was designed and planned, the logrank test was felt to be the most appropriate method for testing the primary hypotheses and so each of the cohorts has been powered on this

basis. However, since that time, there has been increasing evidence that the effect of aspirin on disease-related outcomes may lead to non-proportional hazards and, in particular, the possibility of a 'late effect' emerging.[38,44] Since the design of the Add Aspirin trial, a number of alternative tests have been proposed which are potentially more powerful in this setting.[99, 116] However, as yet, an optimal or most appropriate alternative test, with fully described operating characteristics and appropriate estimates of effect, has not emerged. Nevertheless, this is a very active area of research and we expect such a test (or tests) to emerge prior to the primary analyses of the Add-Aspirin cohorts. If that is the case, the analysis plan will be updated to specify this test, rather than the logrank test, to be used to assess the primary hypotheses in Add Aspirin. This decision will be made by the Trial Steering Committee (who remain blind to the accumulating data), rather than the Independent Data Monitoring Committee (IDMC) and will be formally updated in the analysis plan prior to analysis.

Sample size calculations for the individual cohorts are given in section 10.4. In addition to the main sample size calculations, for each cohort we have also calculated the power of the logrank test with the calculated sample size assuming a delayed effect of aspirin emerging after the first 2 years (with the mean hazard ratio from the start of the study to the time of analysis being equal to the targeted hazard ratio). This might be seen to reflect a "worst case scenario", since we would hope to identify a more powerful test for the primary analyses.

10.3.2 COMBINED ANALYSIS OF OVERALL SURVIVAL

The later analysis of overall survival across the cohorts combined will utilise the same methods as for the cohort-specific primary outcome data. Power calculations for this analysis are given in section 10.4. For these, 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. As noted above, a more optimal test may emerge over time and, in that case, the analysis plan will be updated to reflect this.

For this later analysis, data from the Add-Aspirin trial may be combined in a meta-analysis with data from other trials of aspirin in the adjuvant setting being conducted internationally. This will be dependent on the timelines for reporting each of the individual trials, and the details will be confirmed in a separate analysis plan.

10.3.3 SUBGROUP ANALYSES BY PIK3CA MUTATION STATUS

Published data from recent studies[25,27] 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[103], 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.

It is possible that the results of other trials investigating aspirin use in PIK3CA mutated colorectal cancer (specifically ALASCCA and SAKK 41/13) may be available prior to the primary analysis of the Add-Aspirin colorectal cohort. If this is the case, and depending on the findings from these trials, there may be an interim analysis of the Add-Aspirin data, considering the impact of PIK3CA mutation status.

10.4 SAMPLE SIZE AND POWER

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. Additionally, within the prostate cohort, the radiotherapy and prostatectomy groups are separately 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 the proportional hazards assumption to ensure adequate power using the logrank test to demonstrate effects of aspirin (specified as target hazard ratios) on the primary outcome measures. Power is set at 90% 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.

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 in the control arm, and this will be monitored throughout the trial. 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. In order to reach the target number of randomisations, we anticipate registering at least 11,000 participants for the run-in period (assuming at least 10% drop-out following the run-in).

As noted above, in addition to the main sample size calculations, for each cohort, the power of the logrank test with the calculated sample size and assuming a delayed effect of aspirin emerging after the first 2 years is also indicated.

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,[104] BIG 02-98[105] and GEICAM[106]), as well as results from the recent Indian study of pre-operative progesterone[107], 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 275 control arm IDFS events (717 events in total) to be observed. 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 10% of randomised participants by the time of analysis, the anticipated sample size needed to observe this number of events is approximately 3100 randomised participants. We expect to register at least 3450 breast cancer participants for the run-in period to allow for at least 10% not proceeding beyond that stage.

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[108] and QUASAR[109]), 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 336 control arm DFS events (899 events in total) to be observed. 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 10% of randomised participants by the time of analysis, the anticipated sample size needed to observe this number of events is approximately 2600 randomised participants. We expect to register at least 2890 colorectal cancer participants for the run-in period to allow for at least 10% not proceeding beyond that stage

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[110] and MRC OE02[111] (trials of pre-operative chemotherapy in oesophageal cancer), a US trial of post-operative chemoradiation in gastric and junctional tumours[112] and the MAGIC trial[113] (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[114]. 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 402 control arm deaths (1120 deaths in total) to be observed. 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 10% of randomised participants by the time of analysis, the anticipated sample size needed to observe this number of events is approximately 2100 randomised participants. We expect to register at least 2340 gastro-oesophageal cancer participants for the run-in period to allow for at least 10% not proceeding beyond that stage. The proportion of patients entering with a R1 resection will be monitored over time and the sample size reviewed accordingly.

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,[39] 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 randomised 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[115]. Assuming proportional hazards, a total of 96 control arm bRFS events (230 events in total) will be required to detect this effect with 90% power. The corresponding anticipated sample size is approximately 920 randomised participants.

In the radical radiotherapy group, based on data on intermediate and high-risk patients in RT01 (a recent trial of escalated-dose conformal radiotherapy),[116] 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 173 control arm bRFS events (443 events in total) will be required to detect this effect with 90% power. The corresonding anticipated sample size is approximately 1200 randomised participants.

Thus, the prostate cohort will recruit approximately 2120 randomised participants in total (prostatectomy and radiotherapy groups combined), and we would expect to register at least 2360 prostate cancer patients for the run-in period to allow for at least 10% not proceeding beyond that stage. The 5-year bRFS in the two control arms combined is expected to be approximately 69%. With the planned 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, planned to take place 10 years after the last 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,[104] BIG 02-98[105] and GEICAM[106]) 5-year OS in the control group is expected to be 90%.
- In the colorectal cohort, data from the MOSAIC[108] and QUASAR[109] 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[115] trial in patients receiving radical prostatectomy, along with the results of the RT01[116] 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 ADDITIONAL POWER CALCULATIONS FOR OTHER KEY ANALYSES

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

Data from recent trials[25,27] 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,[117] as well as data on rates of cardiovascular disease in men with prostate cancer from a large population-based study in Sweden,[118] 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 10 years after the last 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.[72] 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. The confidential sections of these analyses (containing data presented by treatment arm) will be available to the IDMC only (and the trial Statisticians who have prepared the report). The IDMC Charter 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. During the course of the trial, an important part of monitoring will be reviewing any new results being made available from other ongoing trials of aspirin as a cancer therapy (see section 1.6). These may affect the timing or plans for analysis of Add-Aspirin data. Any such changes will be discussed and agreed with the IDMC and TSC as appropriate. Permission may also be sought from the IDMC to release data relating to completed sub-studies, the run-in period, 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 incorporated a formal assessment of feasibility, approximately 2 years after the first recruited patients, assessing recruitment feasibility, treatment adherence and safety based on data from the open-label, active run-in period. This phase has now been completed and the trial continues as planned.[1]

At this time, as in their regular reviews, the IDMC reviewed all trial data, but with a particular focus on recruitment, treatment tolerability and adherence. The committee confirmed that there were no safety concerns, and that the trial should continue as planned. Data from this review were released for presentation/publication. Use of the run-in period was also reviewed at this time, and it was agreed that this should remain a part of the protocol.

The IDMC will make recommendations to the TSC and TMG regarding continuation of the trials at each subsequent review, and may choose to release some of the data to them if appropriate.

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 in the control arm.

Following the four cohort specific analyses, combined analyses across all four cohorts are planned for approximately 10 years after recruitment of the last 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. For UK participants, data collected during the trial period will be supplemented by long-term data from medical records (see section 9.3.1). As noted above, consideration will be given to combining Add-Aspirin trial data with data from other trials of aspirin in the adjuvant setting in a meta-analysis, and this may impact the timing of 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 participants 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. As noted above, analyses looking at treatment efficacy according to PIK3CA mutation status will be performed for all cohorts, subject to funding.

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. The data processing is also carried out in accordance with the European Data Protection Regulation applicable as of May 25th, 2018

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 at UCL, Cancer Trials Ireland or TMC, as appropriate, setting out respective roles and responsibilities.

The centre will inform the MRC CTU at UCL (UK and Irish sites) or the CRO (Indian sites) as soon as they are aware of a possible serious breach of compliance, so that this breach, can, if necessary, be reported as per 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 at UCL or the CRO who will discuss with TMC.

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 and the Republic of Ireland. 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 registries and routinely-collected healthcare databases. 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. This responsibility will be delegated to Cancer Trials Ireland for Irish sites.

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 and in the Republic of Ireland.

EudraCT: 2013-004398-28
CTA:31330/0006/001-0001
UK REC:14/SC/0171

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 for UK sites or the relevant hospital department in Irish sites to obtain the Site Specific Assessment.A copy of the local R&D approval (for UK sites) or Site Specific Assessment (for Irish sites), and of the PIS,Consent Form GP Letter, Patient Introductory Leaflet and Cover Letter, on local headed paper should be forwarded to the MRC CTU at UCL and the CRO for Indian centres before participants are entered.

12 INDEMNITY

The overall 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 and an endorsment to the UCL insurance has been granted for Republic of Ireland 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 Indian patients has been arranged by the TMC as the co-sponsor of the trial in India.

13 FINANCE

In the UK Add-Aspirin is funded by Cancer Research UK, the UK NIHR Health Technology Assessment Programme and MRC CTU at UCL. In the Republic of Ireland, additional funding is provided by Cancer Trials Ireland. In India, Add-Aspirin is funded by the Sir Dorabji Tata Trust.

Bayer Pharmaceuticals AG will provide the blinded IMPs - aspirin 300mg, aspirin 100mg and matching placebos – and the aspirin for the run-in period in the UK. M/s CIPLA will provide aspirin for the run-in period in India.

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 4.

14.1 TRIAL MANAGEMENT GROUP (TMG)

The TMG comprises the Chief Investigator, other lead Investigators (clinical and non-clinical, and representing the different countries) and staff at the MRC CTU at UCL and Tata Memorial Centre. 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 XIII.

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)

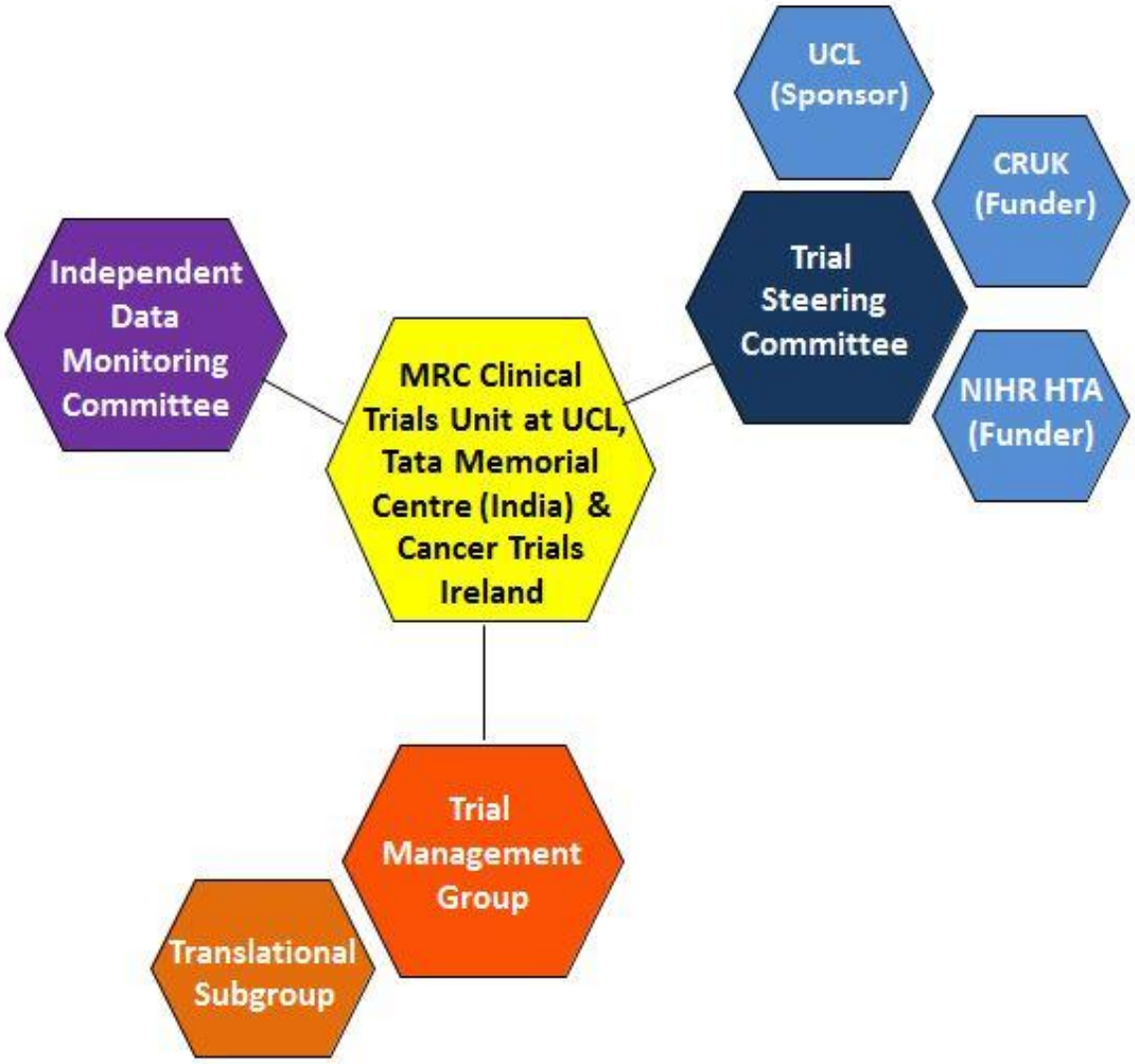
The IDMC will be the only group who sees the confidential, accumulating data for the trial. Reports to the IDMC will be produced by the MRC CTU at UCL. The frequency of IDMC meetings will be determined by the committee and detailed in the IDMC Charter. The IDMC will consider data using the Statistical 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 at UCL. UCL and Tata Memorial Centre are co-sponsors of the trial in India.

Figure 4: 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 5.0 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.

16.1.4 AMENDMENTS MADE TO PROTOCOL VERSION 4.0 13-NOV-2014

1. Throughout- version and date updated to v5.0, 12-Dec-2016
2. Throughout- updates to include details of randomisation, SAE reporting, and TMC & CRO contact details for India.
3. Trial Assessment Schedule-
   - Clarification on the level of flexibility on schedules of assessments and follow up.
   - Updated guidance on timing of blood tests for all cohorts.
   - CRFs included at each timepoint.
4. Section 3-Updates to eligibility criteria for clarification as follows:
   - Clarification of criteria 6 of the breast cohort inclusion criteria.
   - Updated guidance in regard to previous aspirin and NSAID use in all cohort exclusion criteria.
   - Update to acceptable previous malignancies in all exclusion criteria.
   - Clarification regarding co-enrolment into other trials.
   - Update to allow for an R1 resection with circumferential margin microscopically positive within 1mm in patients who have undergone an oesophagectomy or oesophagogastrectomy .
   - Update on timing of entry for gastro-oesophageal cohort
5. Section 4
   - Updated guidance regarding the 'completion of chemotherapy' in the trial registration timelines.
   - Updated timelines for trial entry for patients in the gastro-oesophageal cohort undergoing definitive chemoradiation followed by an endoscopy.
6. Section 5
   - Updated guidance for participants with hypertension
   - Updated guidance for management of gastrointestinal bleeding
   - Updated guidance for management of other toxicities
7. Section 6- Addition of International Physical Activity Questionnaire (IPAQ) at the 12 and 60 months follow up visits

8. Section 7 – clarification around Notable Event reporting
9. Section 9 – Clarification around Thromboxane sub-study
10. Other administrative changes:
    - Update of the MRC CTU at UCL trial administration contacts and Trial Management Group list
    - Correction of any administrative/formatting errors
    - Updated with ISRCTN and CTA numbers
    - Updated with Indian CTRI number
    - Updated name of cognitive assessment to 'MOCA-blind'.
11. Appendices merged with protocol

16.1.5 AMENDMENTS MADE TO PROTOCOL VERSION 5.0 12-DEC-2016

1. Throughout – version and date updated to v6.0, 25-Jul-2019.
2. Throughout – minor typographical corrections and amendments for consistency and clarity.
3. Inclusion of colorectal and prostate cohorts in India.
4. Inclusion of Republic of Ireland specific processes.
5. Inclusion of POLEM collaboration specific information.
6. Page v – trial contact details updated.
7. Page vii – clarification regarding the feasibility phase.
8. Page xii - Flexibility of schedules and Follow Up – clarification regarding blood pressure checks..
9. Trial Assessment Schedules – clarifications regarding imaging for breast and colorectal cohort.
10. Section 1.2.2 – update of clinical evidence: meta-analyses of cardiovascular trials.
11. Section 1.2.3 – update to rationale for colorectal cancer.
12. Section 1.3.3 – update to rationale for gastro-oesophageal cancer.
13. Section 1.6 – update to information regarding ongoing studies.
14. Section 1.8 – addition to objective.
15. Section 3.1-3.8 – clarifications to inclusion and exclusion criteria.
16. Section 3.7 - addition of registration requirements for PSA value in the prostate cohort.
17. Section 4.2 – clarifications to timing of entry for all cohorts.
18. Sections 4.2.2, 4.2.3 and 4.2.4 - extensions made to the colorectal, gastro-oesophageal and prostate cohort minimum entry window in the surgical pathways for India only.
19. Section 4.2.3 – extension of timing of entry for gastro-oesophageal cohort and addition of additional pathways to gastro-oesophageal timing of entry.
20. Section 4.4 – clarification regarding co-enrolment.
21. Section 5.2 – recommendation for prescription of PPI in over 75s.
22. Section 5.4.3.C – clarifications on management of toxicities.
23. Section 6.2 – clarification around the run-in period and randomisation.
24. Section 6.3 – addition of information regarding biochemical failure in the prostate cohort.
25. Section 6.9 – addition of survivorship questionnaire.
26. Section 6.10 – clarification regarding early stopping of follow-up, and addition of annual visit in India and Republica of Ireland between years 6-10.
27. Section 7.2.2 – clarification regarding notable events.
28. Section 7.3.2 – addition of galaxkey as method of notification of SAEs.
29. Section 9.1 – clarifications regarding the thromboxane B_2 study.
30. Section 9.2 – clarifications regarding sample collection procedures.
31. Section 9.3.2 – addition of participant newsletter methodology study.
32. Section 10.4 – clarification regarding timing of analysis.

33. Section 10.6 – clarification regarding the feasibility phase.
34. Section 11.1.1 – addition of GPDR.

16.1.6 AMENDMENTS MADE TO PROTOCOL VERSION 6.0 25-JUL-2019

1. Trial Summary – clarification in study design section regarding the addition of future comparisons.
2. Section 6.9 (and schedules) – removal of Survivorship Questionnaire.

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.

16.2.4 AMENDMENTSMADE TO APPENDICIES VERSION 4.0 13-NOV-2014

1. The Add-Aspirin Patient Information Sheet and Informed Consent Form have been amended to clarify what personal data we are collecting from patients.
2. Informed Consent Form updated with optional consent for urine samples
3. PIS updated to reflect that not all CT scans are necessarily standard of care at every participanting site.
4. PIS updated with additional information regarding travel insurance for participants on a trial.
5. GP letter amended to remove '…and a list of drug to be avoided' for clarity.
6. Addition of Participant Introductory Leaflet for optional use at sites to give to patients prior to PIS.
7. Addition of Cover Letter for PIS for optional use at sites to post PIS to patients not regularly attending clinic.
8. Inclusion of trial entry timing diagrams to appendices.

16.2.5 AMENDMENTSMADE TO APPENDICIES VERSION 5.0 06-DEC-2016

1. The Add-Aspirin Patient Information Sheet has been updated to include additional information on unblinidng.
2. Addition of information in the PIS about a survivorship questionnaire at the end of randomised treatment (60 month visit) for all patients.
3. PIS updated to provide additional information on PPi administration.
4. Updates to the PIS about how participants data is held in line with GDPR.
5. PIS updated to give information aboutadditional blood samples at 3 time points that may be taken in sites participating in the sub-study.
6. Clarficiations made to the informed consent form relating to the use of samples.
7. GP letter has been amended to add in details about the run-in phase, and dosage for patients over 75.
8. A new Patient Urine Sample Leaflet has been created to assist patients participating in the urine sub-study.

16.2.6 AMENDMENTSMADE TO APPENDICIES VERSION 6.0 25-JUL-2019

1. Removal of information in the PIS about the survivorship questionnaire.
2. Creation of a Transparency notice for patients.

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APPENDICES

APPENDIX I – 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 II – 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 III – 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 IV – COLORECTAL TUMOUR STAGING GUIDELINE

For patients with colon or rectal cancer who do not have any neoadjuvant treatment, eligibility is based on the histological staging from the resection specimen.
For patients with rectal adenocarcinoma that have neoadjuvant treatment (chemoradiotherapy or radiotherapy alone) eligibility is based on the radiological staging prior to starting neoadjuvant treatment.

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 V – 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 VI – 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

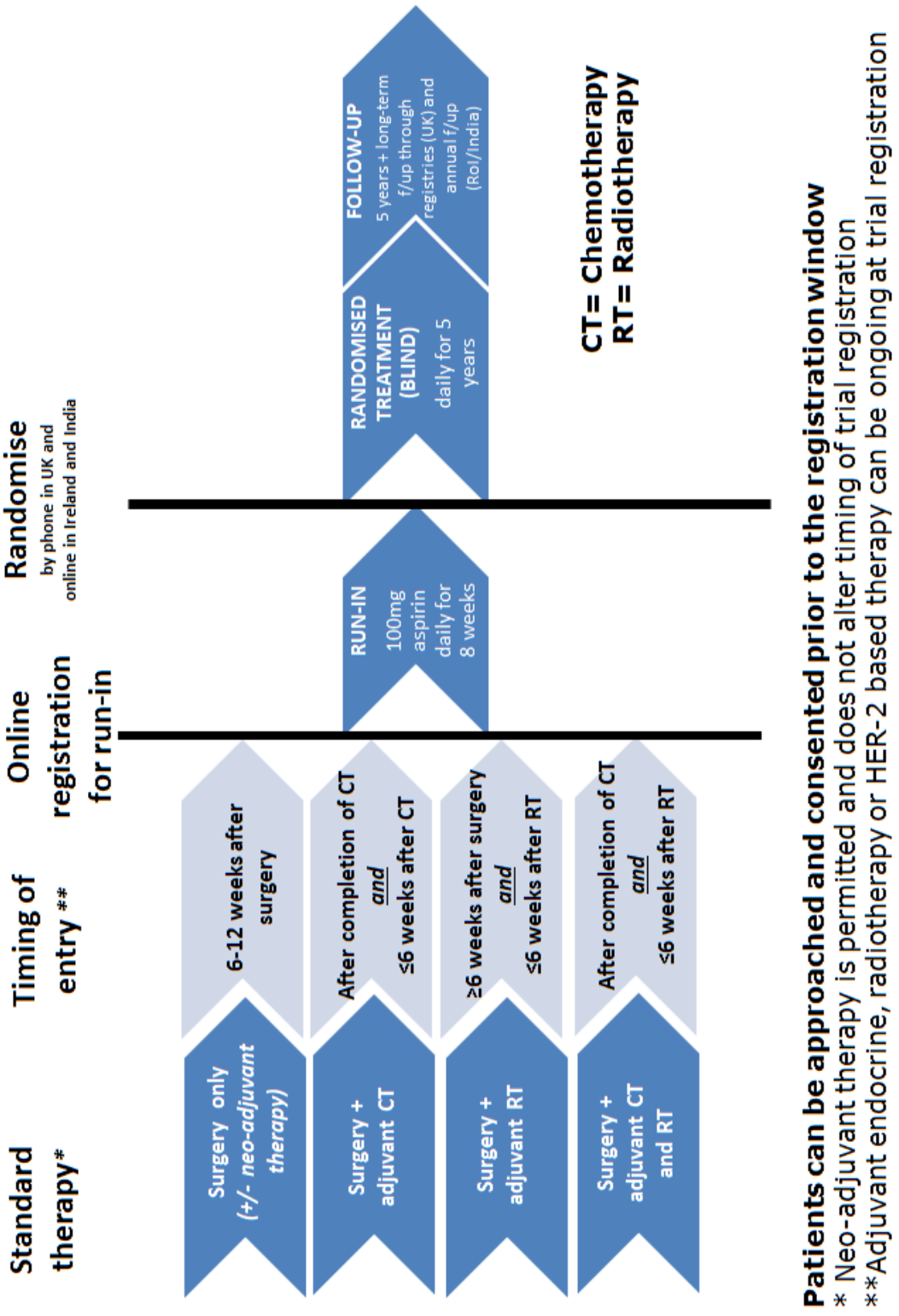
From the 7th edition of the AJCC TNM staging manual.

APPENDIX VII – PROSTATE CANCER STAGING

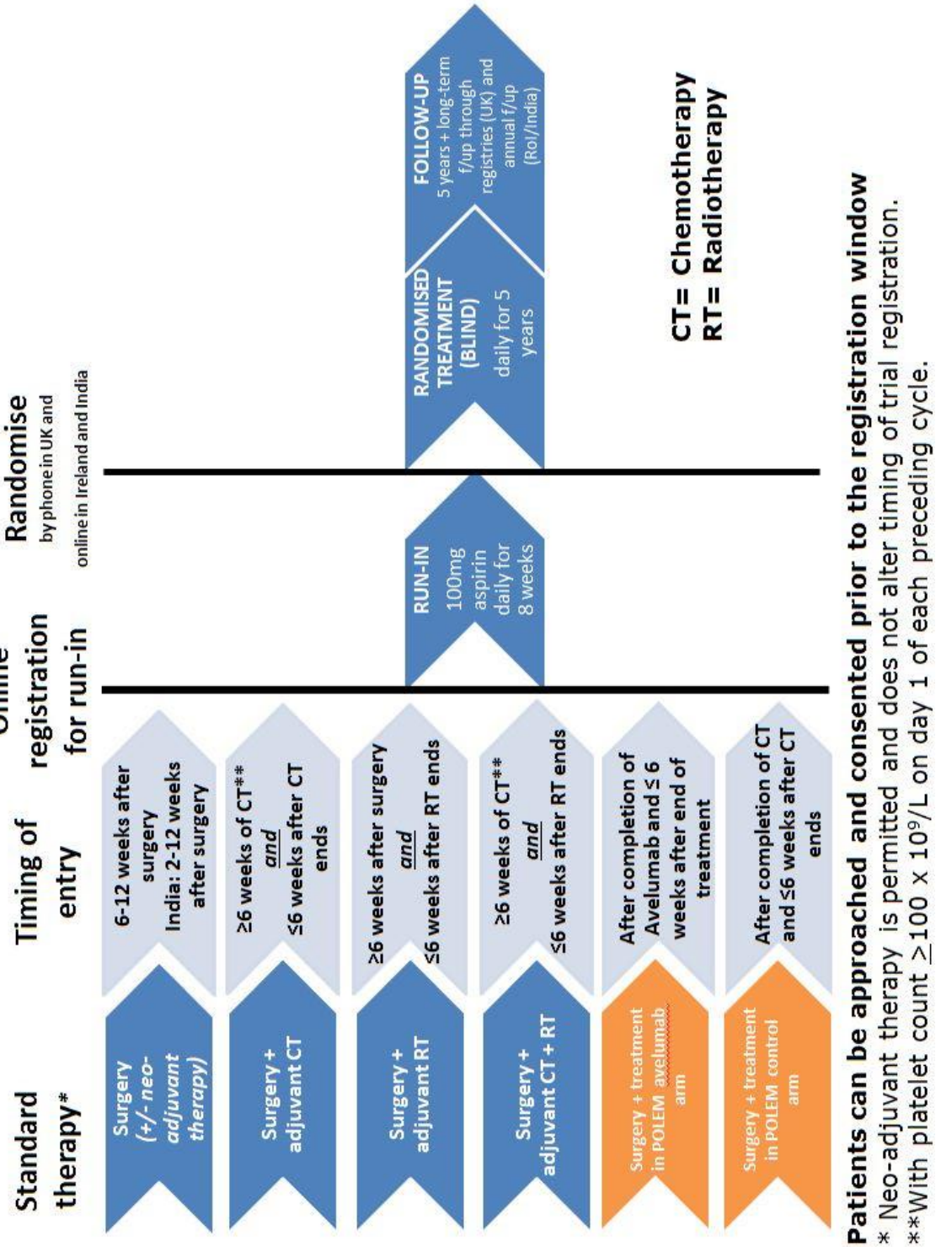
Anatomic stage/Prognostic groups					
Group	T	N	M	PSA	Gleason
I	T1a-c	N0	M0	PSA<10	Gleason ≤6
	T2a	N0	M0	PSA<10	Gleason ≤6
	T1-2a	N0	M0	PSAX	Gleason X
IIA	T1a-c	N0	M0	PSA<20	Gleason 7
	T1a-c	N0	M0	PSA≥10<20	Gleason ≤6
	T2a	N0	M0	PSA≥10<20	Gleason ≤6
	T2a	N0	M0	PSA<20	Gleason 7
	T2b	N0	M0	PSA<20	Gleason ≤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 VIII – BREAST COHORT TIMING OF ENTRY



APPENDIX IX – COLORECTAL COHORT TIMING OF ENTRY



APPENDIX X – GASTRO-OESOPHAGEAL COHORT TIMING OF ENTRY

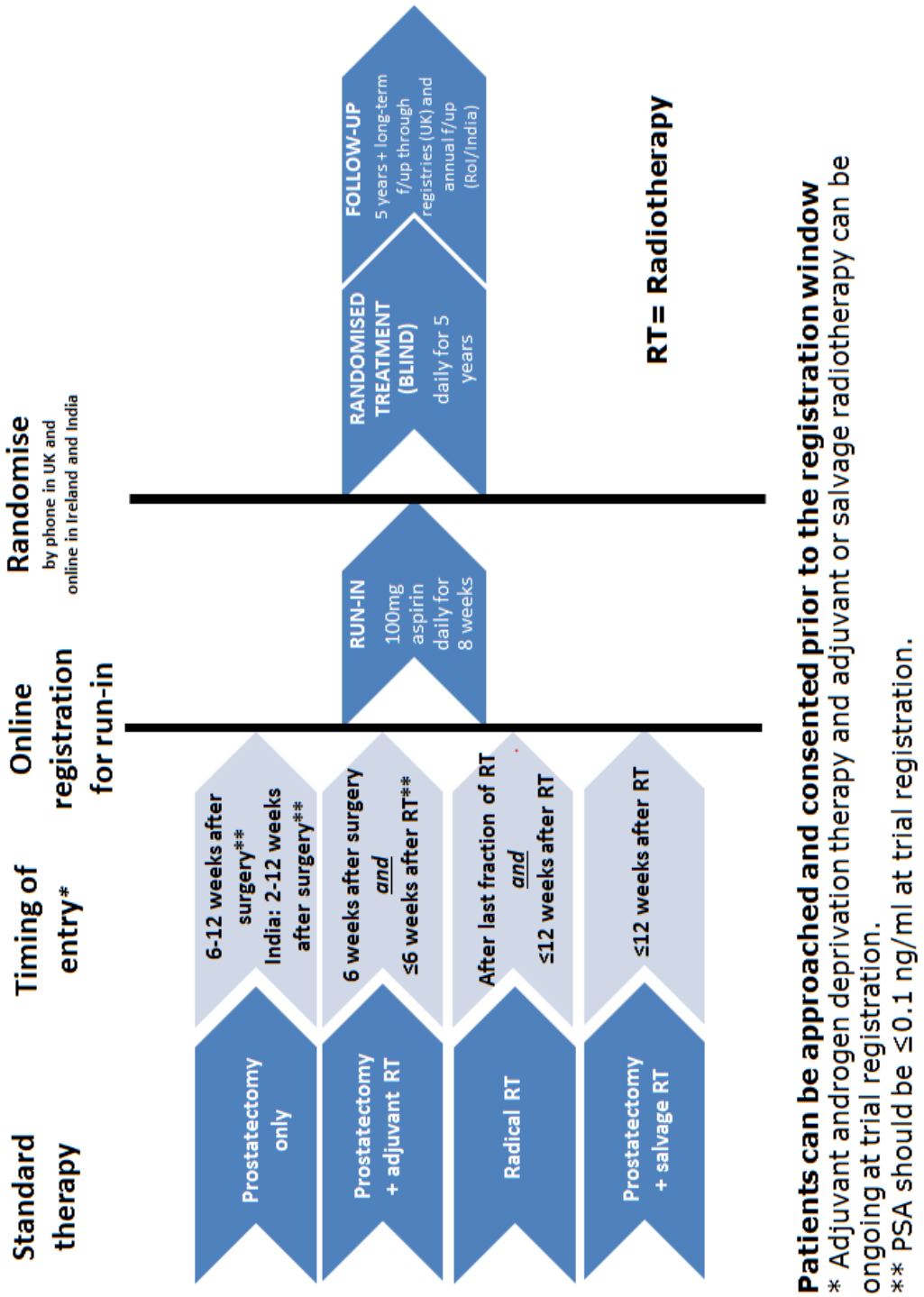
Patients can be approached and consented prior to the registration window

* Neo-adjuvant therapy is permitted and does not alter timing of trial registration.

**If registration takes place whilst chemotherapy is ongoing, platelet count should be ≥100 x 10^9/L on day 1 of each preceding cycle.

***Patients having a routine endoscopy at 12 weeks after CRT can register up to 4 weeks after this has been performed.

APPENDIX XI – PROSTATE COHORT TIMING OF ENTRY



APPENDIX XII – CRF COMPLETION SCHEDULE

Months since randomisation (except where indicated)														
Form Number and Name[1]	Prior to Registration	Prior to randomisation (*end of run-in period*)	*3*	*6*	*9*	*12*	*18*	*24*	*30*	*36*	*42*	*48*	*54*	*60*
Participant Consent Form	✓													
*1bc, 1cc, 1gc **or** 1pc – Cohort-specific Registration Form (as applicable)*	✓													
2 – Sample Collection Form	✓													
2a – Urine Collection CRF	✓	✓	✓											
3 – Baseline Characteristics CRF	✓													
4 – Comorbidities	✓													
5 – Functional Status (Only participants >65 years of age at registration)[2]	✓													✓
6 – Cognitive Assessment[2]	✓					✓								✓
7 – End of Run-In Period + Randomisation		✓												
7a – End of Run-In Extension + Randomisation (if applicable)		✓												
8 – Follow-Up CRF			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
*8bc, 8cc, 8gc **or** 8pc –Cohort specific Follow-Up CRF*			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

[1] Form numbers in India will be followed by the letter 'i'

[2] In the UK and Republic of Ireland only.

APPENDIX XIII– TRIAL MANAGEMENT GROUP AND COLLABORATORS

Gastro-oesophageal Cohort		
Professor Ruth Langley	Chief Investigator Lead Investigator – Gastro-oesophageal Cohort (UK)	London, UK
Professor C 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
Professor Tim Underwood	Surgeon – Gastro-oesophageal Cohort	Southampton, UK
Professor Anne Thomas	Medical Oncologist – Gastro-oesophageal Cohort	Leicester, UK
Professor John Bridgewater	Medical Oncologist – Gastro-oesophageal Cohort	London, UK
Dr Chris Coyle	Medical Oncologist	Portsmouth, UK
Professor Seamus O'Reilly	Lead Investigator – Gastro-oesophageal Cohort (Ireland)	Cork, Ireland
Verity Henson	Clinical Trials Officer	Bristol, UK
Anne Crossley	Clinical Trials Nurse	Leeds, UK
Yvonne Carse	Participant representative	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
Dr Janice Walshe	Lead Investigator – Breast Cohort (Ireland)	Tallaght, Ireland

Mairead MacKenzie	Participant Representative, Independent Cancer Patient Voices	UK
Colorectal Cohort		
Professor Richard Wilson	Lead Investigator – Colorectal Cohort	Glasgow, UK
Dr Tim Iveson	Medical Oncologist – Colorectal Cohort	Southampton, UK
Professor Robert Steele	Surgeon – Colorectal Cohort	Dundee, UK
Dr Dan Swinson	Clinical Oncologist – Colorectal Cohort	Leeds, UK
Miss Farhat Din	Surgeon – Colorectal Cohort	Edinburgh, UK
Dr Janet Graham	Medical Oncologist – Colorectal Cohort	Glasgow, UK
Dr Avanish Saklani	Lead investigator – Colorectal Cohort (India)	Mumbai, India
Dr Gregory Leonard	Lead Investigator – Colorectal Cohort (Ireland)	Galway, Ireland
Anne Crossley	Clinical Trials Nurse	Leeds, UK
Verity Henson	Clinica Trials Officer	Bristol, UK
Lindy Berkman	Participant Representative, NCRI Consumer Liaison Group	UK
Sue Campbell	Participant representative	UK
POLEM Study Collaborators (CRC)		
Dr Tony Dhillon	POLEM Study Chief Investigator	RMH
Professor David Cunningham	POLEM Co-investigator	RMH
Dr Naureen Starling	POLEM Co-investigator	RMH
Prostate Cohort		
Professor Howard Kynaston	Lead Investigator – Prostate Cohort	Cardiff, UK
Dr Duncan Gilbert	Clinical Oncologist – Prostate Cohort	Brighton, UK
Dr Ganesh Bakshi	Lead Investigator – Prostate Cohort (India)	Mumbai, India
Professor Raymond McDermott	Lead Investigator – Prostate Cohort (Ireland)	Tallaght, Ireland

Arnold Goldman	Participant Representative	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
Dr Durga Gadgil	Clinical Consultant, TMC	Mumbai, 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
Sue Campbell	Participant representative	UK
MRC CTU at UCL		
Tessa Dibble	Trial Manager	MRCCTU at UCL, UK
Ben Sydes	Data Manager	MRCCTU at UCL, UK
Malissa Richmond	Data Manager	MRCCTU at UCL, UK
Peter Skoutari	Data Manager	MRCCTU at UCL, UK
Sangeetha Kunaseelan	Trial Assistant	MRCCTU at UCL, UK
Dr Fay Cafferty	Project Leader/Senior Statistician	MRCCTU at UCL, UK
Lynda Harper	Clinical Project Manager	MRCCTU at UCL, UK
Dr Nalinie Joharatnam	Clinical Research Fellow/Trial Physician	MRCCTU at UCL, UK

We would like to acknowledge the contribution of Dr Geoffrey Venning towards initiating this project. His foresight, patience and wisdom are appreciated.

APPENDIX XIV– POLEM TRIAL COLLABORATION *(AT SELECTED APPROVED CENTRES)*

1 BACKGROUND

Collaboration Rationale

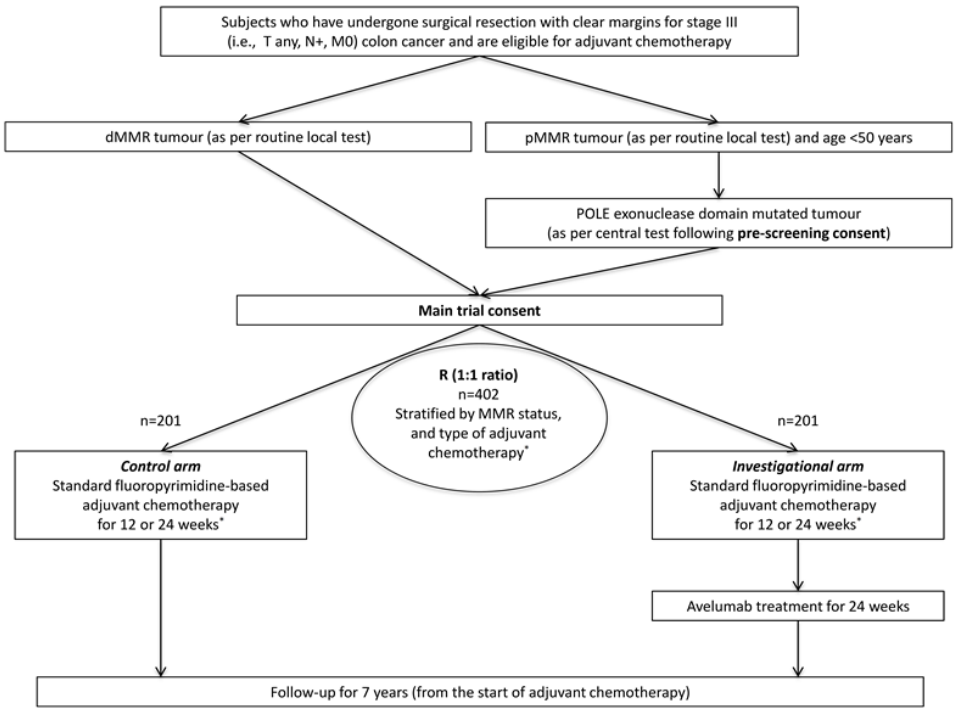
Both the Add-Aspirin and POLEM trials are aiming to improve outcomes after radical treatment for colorectal cancer, and will be recruiting from the same group of patients. The Add-Aspirin Colorectal–POLEM collaboration provides an opportunity for centres, not currently participating in the POLEM trial, to enable their patients to have improved access to multiple trials. Centres are encouraged to screen patients for potential entry into POLEM, and subsequent entry into Add-Aspirin. The collaboration provides an opportunity for these rarer patients to have access to new drugs. The collaboration also aims to streamline the recruitment process and align the follow-up schedules for the two trials in order to improve recruitment and retention, and enable results to be published sooner.

POLEM Rationale

The purpose of the POLEM trial is to determine if DNA Mismatch Repair deficient (dMMR) and/or POLE exonuclease domain mutant stage III colon cancer patients gain clinical benefit (i.e. improvement in disease free and overall survival) from PD-L1 inhibitors after standard fluoropyrimidine-based adjuvant chemotherapy.

The rationale of giving Avelumab after standard adjuvant chemotherapy to this well-defined, molecularly-selected, group developed from evidence suggesting that dMMR and POLE exonuclease domain mutant colon cancers have a highly and ultra-mutated genetic profile, respectively, thus leading to a high number of neo-antigens with associated over expression of immune checkpoint related proteins. This profile is expected to be highly responsive to checkpoint inhibition as suggested by data of PD-1 inhibitors in dMMR/MSI-H metastatic CRCs.

POLEM Trial Flow Chart



*The choice of type and duration of adjuvant chemotherapy is left to the discretion of the local investigator. However, this has to be declared before randomisation. Allowed regimens include:
- 8 cycles of 3-weekly capecitabine
- 4 cycles of 3-weekly capecitabine and oxaliplatin according to the CAPOX regimen

POLEM Trial Summary

POLEM is an open-label, multi-centre, randomised, phase III trial comparing standard fluoropyrimidine-based adjuvant chemotherapy followed by avelumab (experimental arm) with standard fluoropyrimidine-based adjuvant chemotherapy alone (control arm) in patients who have undergone radical surgical resection for stage III dMMR or *POLE* exonuclease domain mutant colon cancer. Patients will be stratified in a 1:1 ratio for dMMR status and type of adjuvant chemotherapy (i.e., 24 weeks of single agent capecitabine chemotherapy versus 12 weeks of CAPOX chemotherapy).

402 patients (201 per arm) are to be randomised. It is expected that approximately 4000 participants will need to be screened in order to recruit 402 patients to the study, assuming an incidence of dMMR of 10-15% and an incidence of *POLE* mutations of 7% in patients under 50 years (unpublished data from Tomlinson group). The study is expected to take up to 36 months to complete accrual.

There are no prescriptive criteria for surgical resection of the primary tumour in this trial. It is however expected that resection of the tumour will be undertaken in the elective setting by a colorectal specialist surgeon.

Tumour MMR status will be routinely tested locally as per NICE guidelines (either in the pre-operative biopsy or resection specimen). Subjects whose tumours are dMMR (lack of staining of at least one of MLH1, MSH2, PMS2 or MSH6 proteins) can sign the main study consent and undergo the study screening procedures. If they are found to fulfil all eligibility criteria, then they will be randomised. At POLEM centres, subjects who are aged below 50 years and whose tumours are pMMR, will be asked to sign a pre-screening consent for the centralised analysis (Oxford Molecular Diagnostics Centre, John Radcliffe Hospital, Oxford) of *POLE* exonuclease domain mutations. However, Add-Aspirin centres who are not fully participating in POLEM will not participate in this aspect of the screening process.

All eligible patients who are randomised will receive standard fluoropyrimidine-based adjuvant chemotherapy for 12 or 24 weeks depending on the decision of the local investigator. The choice of adjuvant chemotherapy (i.e., 24 weeks of single agent fluoropyrimidine chemotherapy or 12 weeks of doublet, oxaliplatin-based chemotherapy) must be declared by the investigator at study entry before randomisation. Type of adjuvant chemotherapy (i.e., 24 weeks of single agent capecitabine or 12 weeks of capecitabine plus oxaliplatin) will be used as stratification factor alongside MMR status.

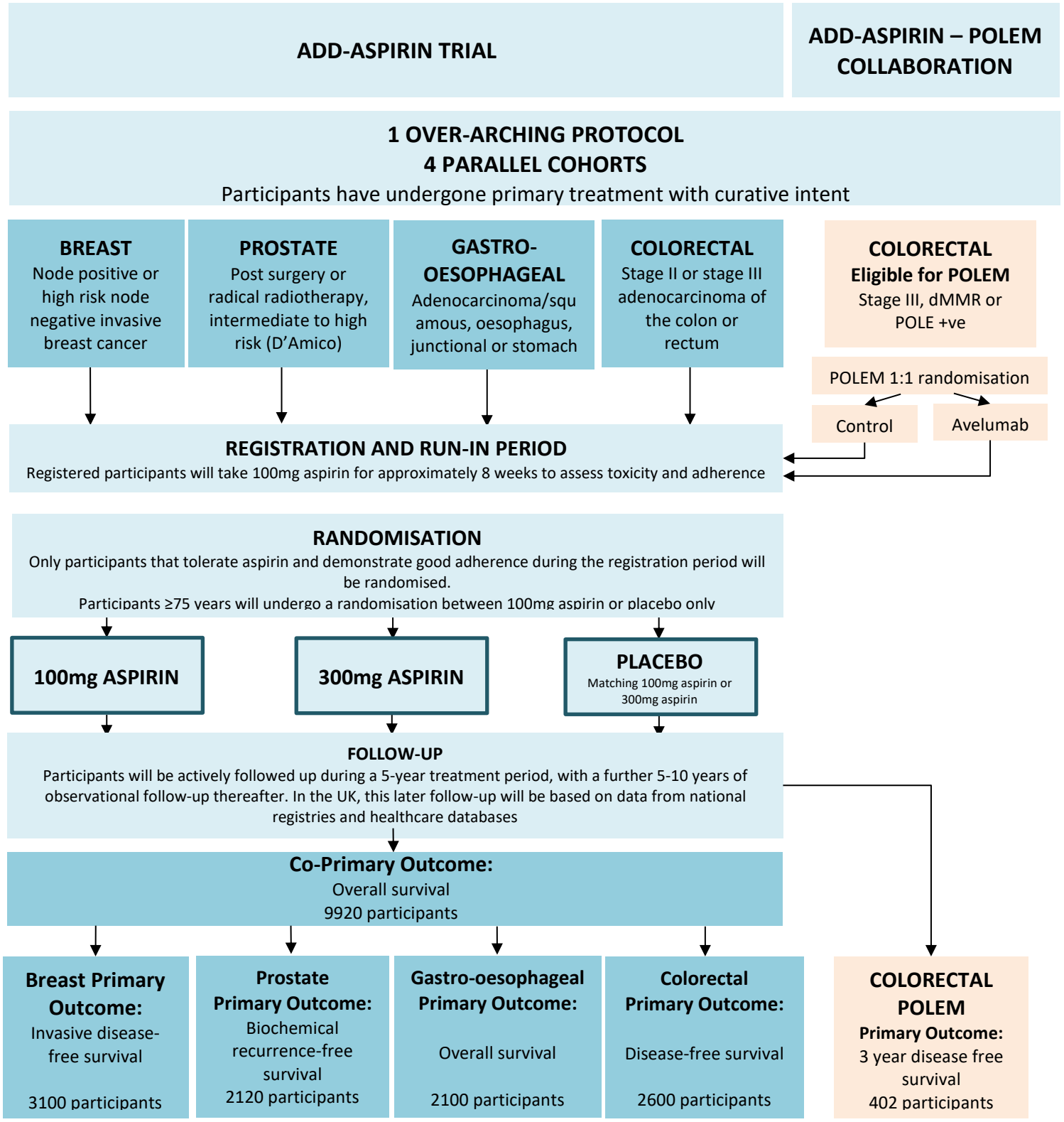
At the end of adjuvant chemotherapy, patients who are randomised to the investigational arm, will receive an additional 24 weeks of treatment with avelumab.

After completion of treatment, all subjects will be followed up for up to 7 years from the start of adjuvant chemotherapy.

Correlative biomarker analyses will be conducted as part of the translational study in tumour tissue samples from the resection specimens, tumour tissue samples from the relapsed tumour (if applicable, feasible and upon patient consent) and serial blood samples collected at study entry, during adjuvant treatment and follow-up.

2 COLLABORATION OVERVIEW

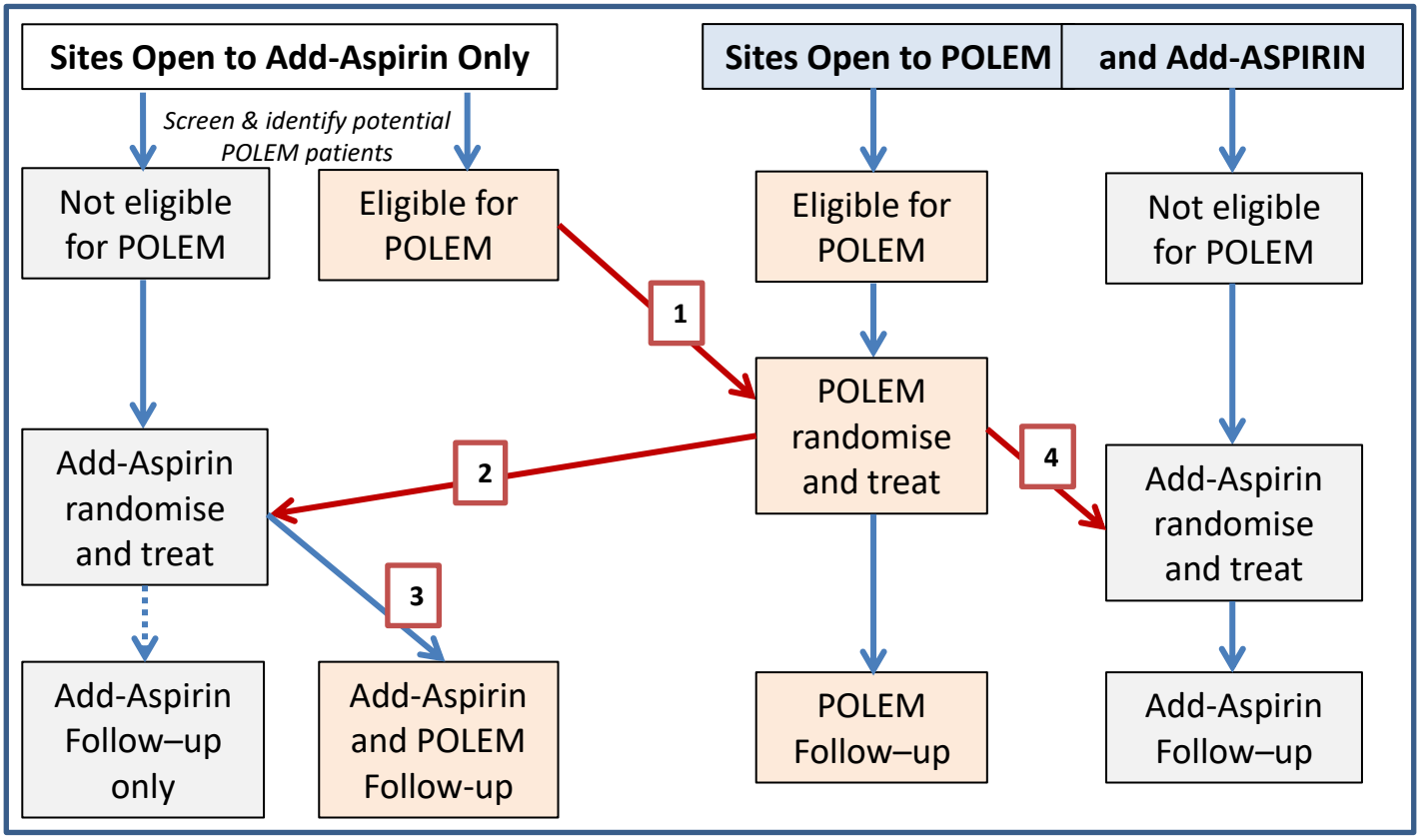
Figure 1: Add-Aspirin Trial Design



Collaboration Overview

The collaboration described in this Appendix (XIV) is largely relavant to Add-Aspirin centres who are not fully participating in POLEM. POLEM centres should follow the POLEM protocol with regards to management, treatment and follow-up of these patients. POLEM centres should offer coenrolment into Add-Aspirin *sequentially*, after randomised treatment with Avelumab/control is completed.

Figure 2: Add-Aspirin-POLEM flow diagram



Add-Aspirin only centres:

1.For centres open to Add-Aspirin only

These centres (selected sites only) are able to perform screening and follow up activities for POLEM. All treatment administration will be at POLEM centres.

1. Identify potential eligible patients with MMR deficiency for POLEM, at colorectal MDTs/new patient clinics.
2. Provide patients with Add-Aspirin – POLEM introductory sheets.
3. If potential eligible patients willing, transfer to nearest POLEM centre. Contact the MRC CTU at UCL to identify your nearest treating POLEM centre.
4. POLEM centre confirms eligibility, consents and screens patient and randomises to Avelumab or control arm plus standard of care adjuvant chemotherapy. (Adjuvant treatment +/- investigational treatment must be administered at the selected POLEM centre.

2. Sequential entry into Add-Aspirin following POLEM treatment:

5. If randomised to Avelumab, consider transferring patient back to referring centre for discussion and randomisation into Add-Aspirin at the end of treatment.

6. If randomised to control arm, transfer patient back to referring centre, following treatment with adjuvant chemotherapy, for discussion and randomisation into Add-Aspirin.

3. Follow-up

7. It is expected that POLEM patients referred by Add-Aspirin centres have ongoing follow-up at the original Add-Aspirin centre, *unless* the POLEM treating centre has any safety concerns. In circumstances where this is not deemed appropriate, please discuss with the MRC CTU.

8. Add-Aspirin centre performs follow up for both trials. For POLEM specific follow up, Add-Aspirin centre will complete CRFs for POLEM and send to POLEM central CTO – the Gastrointestinal (GI) Unit Clinical Trial Office (CTO) and the Royal Marsden Hospital (RMH) (Appendix XIV, section 11).

9. If POLEM patient ineligble/does not enter Add-Aspirin, or does not proceed to randomisation, POLEM follow-up continues at Add-Aspirin referring centre, unless patients remains at POLEM treating centre.

Centres recruiting to Add-Aspirin and POLEM:

4.For centres open to both POLEM and Add-Aspirin

1. Provide patients with Add-Aspirin – POLEM introductory sheets.
2. Patients should complete POLEM screening, randomisation and treatment in accordance with the POLEM protocol.
3. Then consider registration and randomisation into Add-Aspirin sequentially.
4. Follow up occurs as per two coenrolled trial protocols. However timing of entry into Add-Aspirin differs (Appendix XIV, section 6).

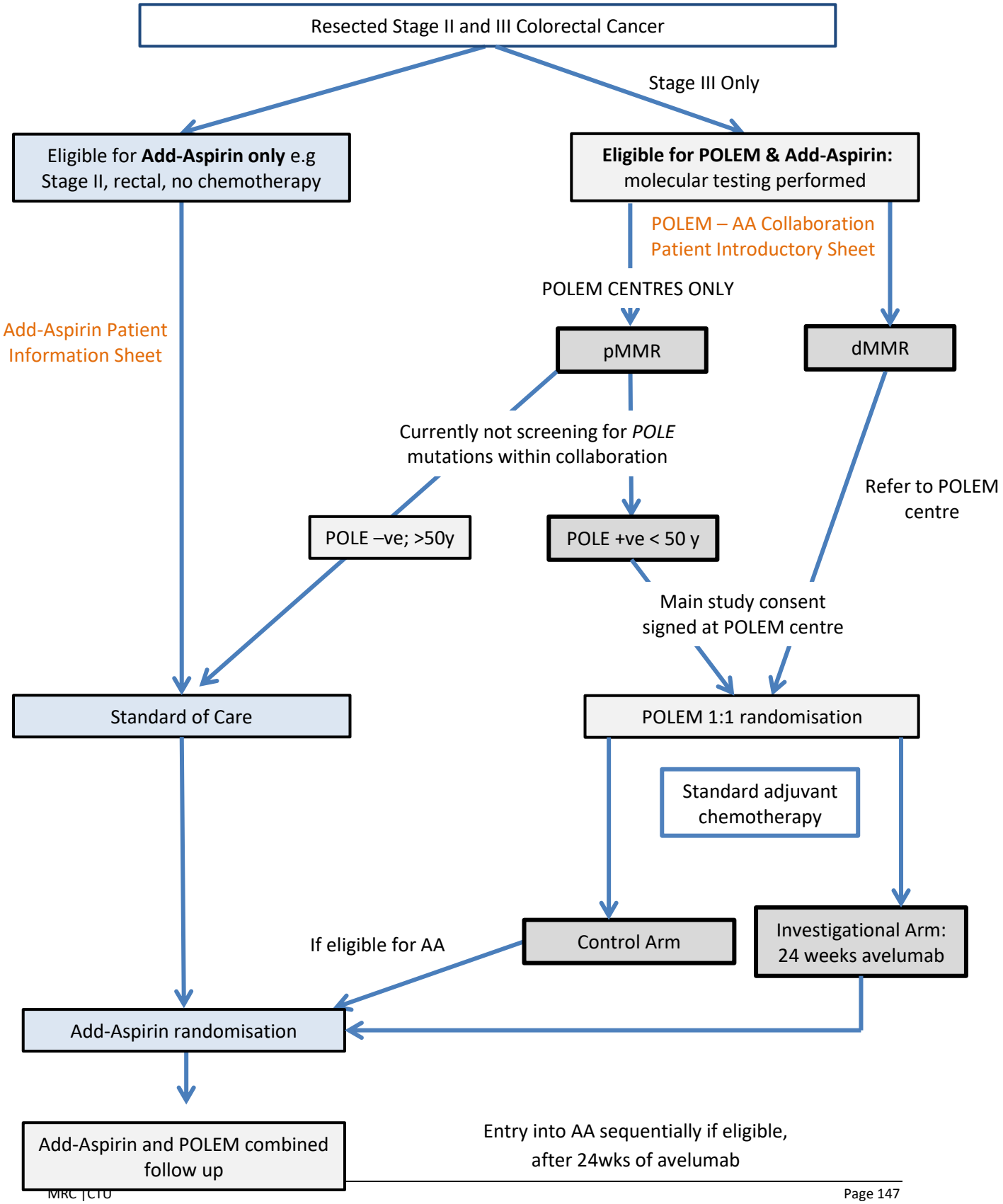
2B) Agreements

For Add-Aspirin centres participating in the collaboration, site agreements will be needed with the RMH GI CTO. Payment(s) will be made for completion of follow-up investigations and sample collection.

3 ELIGIBILITY

3A) Add-Aspirin – POLEM Participant Pathway

Figure 3: Add-Aspirin-POLEM flow diagram



3B) POLEM INCLUSION CRITERIA

Please direct queries regarding POLEM eligibilty to the GI Unit CTO at RMH. Eligible patient details should be sent to the GI Unit CTO at RMH (fax 02086613570; gi.trials@rmh.nhs.uk)

1. Male or female subjects aged ≥18 years

2. ECOG PS 0/1

3. Histologically proven, stage III (i.e., any T, N1 or N2, M0) adenocarcinoma of the colon (as defined by the presence of the inferior pole of the tumour above the peritoneal reflection - that is, at least 15 cm from the anal margin).

4. Fully surgically resected tumour with clear resection margins (i.e., >1 mm)

5. Locally confirmed defective mismatch repair (dMMR) tumour (as defined by the lack of staining on either pre-operative biopsy samples or resection specimens of at least one of the following proteins: MLH1, MSH2, MSH6, PMS2) or centrally confirmed POLE exonuclease domain mutated tumour (in subjects <50 years old with locally confirmed proficient (p)MMR tumours)

6. Absence of metastases as shown by a pre or post-operative CT scan

7. Absence of major post-operative complications or other clinical conditions that, in the opinion of the investigator, would contraindicate adjuvant chemotherapy

8. Adequate haematological function defined by absolute neutrophil count (ANC) ≥1.5 × 10^9/L, platelet count ≥100 × 10^9/L, and haemoglobin ≥9 g/dL

9. Adequate hepatic function defined by a total bilirubin level ≤1.5 × the upper limit of normal (ULN) range and AST and ALT levels ≤2.5 × ULN

10. Adequate renal function defined by an estimated creatinine clearance ≥30 mL/min according to the Cockcroft-Gault formula (or local institutional standard method)

11. Negative serum or urine pregnancy test at screening for women of childbearing potential

12. Fertile men and women must agree to take highly effective contraceptive precautions during, and for 6 months after the last dose of chemotherapy or for 1 month after the last dose of Avelumab

3C) POLEM EXCLUSION CRITERIA

Subjects are not eligible for the trial if they fulfill any of the following exclusion criteria:

1. Rectal tumours (as defined by the presence of the inferior pole of the tumour below the peritoneal reflection - that is, <15 cm from the anal margin).

2. Inability to start adjuvant chemotherapy within 12 weeks after surgery

3. Administration of neoadjuvant systemic chemotherapy or radiotherapy before surgical resection of colon cancer

4. Prior organ transplantation, including allogeneic stem cell transplantation

5. Significant acute or chronic infections including, among others:
- known history of testing positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)
- positive test for HBV surface antigen or anti-HCV antibody and confirmatory HCV RNA test

6. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent:
- Subjects with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible
- Subjects requiring hormone replacement with corticosteroids are eligible if the steroids are administered only for the purpose of hormonal replacement and at doses ≤10 mg/day of prednisone or equivalent
- Administration of steroids through a route known to result in a minimal systemic exposure (topical, intranasal, intro-ocular, or inhalation) are acceptable

7. Known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥3 NCI-CTCAE v 4.0), any history of anaphylaxis, or uncontrolled asthma (that is, 3 or more features of partially controlled asthma)

8. Persisting toxicity related to prior therapy of Grade >1 NCI-CTCAE v 4.0; however, alopecia and sensory neuropathy Grade ≤2 is acceptable unless oxaliplatin administration is planned as part of the adjuvant treatment
9. Pregnancy or lactation

10. Known alcohol or drug abuse

11.Clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke (<6months prior to enrollment), myocardial infarction (<6months prior to enrollment),, unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II),, or serious cardiac arrhythmia requiring medication

12. Prior myocarditis

13. Known history of immune colitis, immune pneumonitis, pulmonary fibrosis or other medical conditions (for example, inflammatory bowel disease, uncontrolled asthma), which, in the opinion of the Investigator, might impair the subject's tolerance of trial treatment

14. Any psychiatric condition that would prohibit the understanding or rendering of informed consent

15. Vaccination within 4 weeks of the first dose of avelumab and while on trial is prohibited except for administration of inactivated vaccines

16. Other invasive malignancy within 2 years except for non-invasive malignancies such as cervical carcinoma in situ, non-melanomatous carcinoma of the skin or ductal carcinoma in situ of the breast that has/have been surgically cured. Cancer subjects with incidental histological findings of prostate cancer (tumour/node/metastasis stage of T1a or T1b or prostate-specific antigen <10) who have not received hormonal treatment may be included, pending a discussion with the study physician

4 TIMING OF ENTRY IN ADD-ASPIRIN FOLLOWING POLEM TREATMENT:

A diagram of the timing of entry criteria for the colorectal cohort is available in appendix IX.

a) **Surgery and entry into POLEM trial - if randomised to adjuvant chemotherapy and Avelumab** (24 week treatment): the Add-Aspirin run-in period can start after completion of Avelumab and no later than 6 weeks after the end of immunotherapy

b) **Surgery and entry into POLEM trial – if randomised to adjuvant chemotherapy alone (control arm):** the run-in period can start after completion of chemotherapy and no later than 6 weeks after the end of chemotherapy.

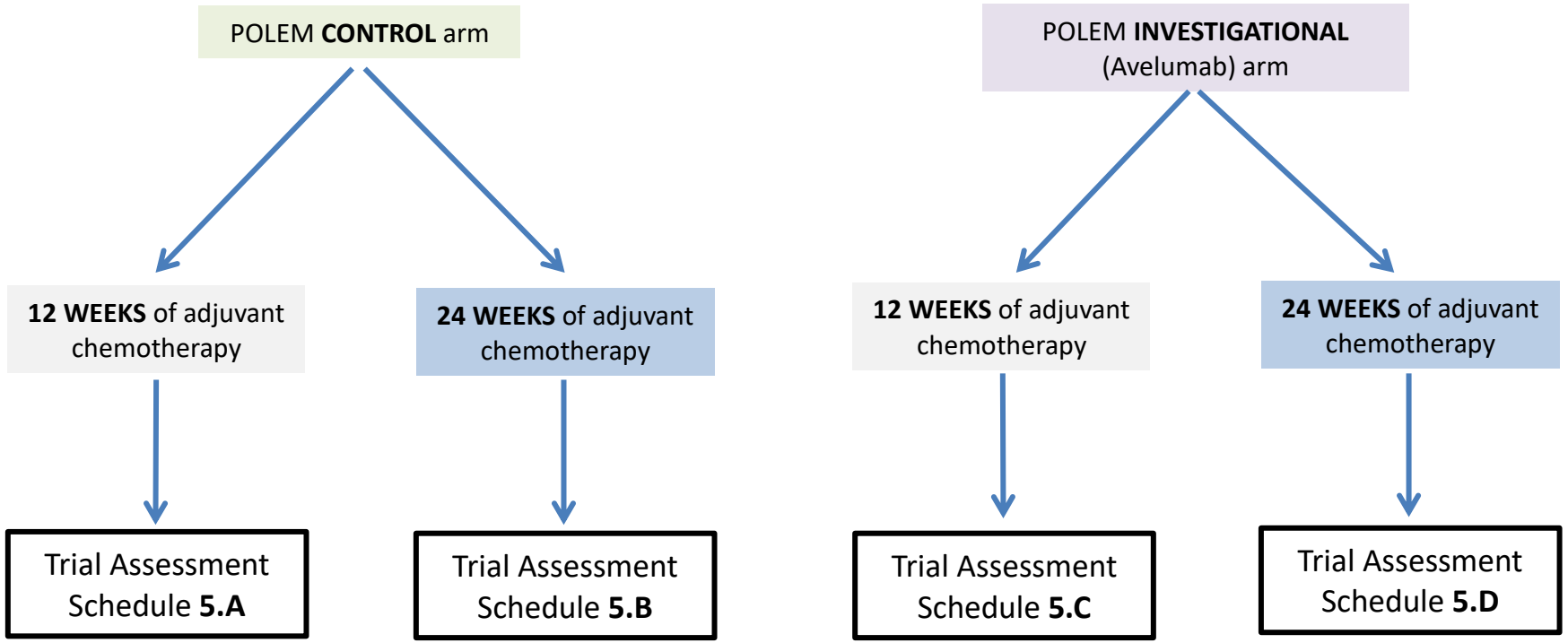
5 ADD-ASPIRIN – POLEM COLLABORATION TRIAL ASSESSMENT SCHEDULE

For patients initially screened at Add-Aspirin centres, POLEM follow-up is expected to be performed at the referring Add-Aspirin centre, in accordance with the schedules below – regardless of subsequent participation in Add-Aspirin. Trial assessment schedules for POLEM and Add-Aspirin have been aligned, as per below. POLEM visits have a window of flexibility, and can occur +/- 1 month in the first year, and +/-3months thereafter. Patients within POLEM are randomised to either a control or investigational (Avelumab) arm.

The choice of type and duration of adjuvant chemotherapy is left to the discretion of the local investigator. Allowed regimens include:

- 8 cycles of 3 weekly capecitabine (24 weeks of treatment)
- 4 cycles of 3 weekly capecitabine and oxaliplatin according to the CAPOX regimen (12 weeks of treatment)

The follow-up assessment schedule varies according to whether patients have had 12 weeks of adjuvant chemotherapy or 24 weeks. The following diagram illustrates which trial assessment schedule to follow based on randomisation and duration of chemotherapy:



5.A) Add-Aspirin – POLEM Collaboration Trial Assessment Schedule (Colorectal Cohort)
For Patients in the CONTROL Arm on 12 WEEKS of adjuvant chemotherapy (CAPOX)

AA VISITS	MONTHS SINCE ADD-ASPIRIN RANDOMISATION	AA CRF NUMBER	PRIOR TO REGISTRATION	PRIOR TO RANDOMISATION (END OF RUN-IN PERIOD)	3M	6M	9M	12M	18M	24M	30M	36M	42M	48M	54M	60M	-	-
POLEM VISITS	**MONTHS SINCE START OF ADJUVANT CHEMOTHERAPY**		**END OF TREATMENT VISIT[1b]**	**6M**	**9M**	**12M**		**18M**	**24M**	**30M**	**36M**		**48M**		**60M**		**72M**	**84M**
Main assessments	AA Registration assessments[1a]	**1cc, 3, 4, 16***	✓															
	AA End of run-in assessment[2]	**7**		✓														
	Follow-up assessment[3]	**8, 8cc**			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Imaging and procedures	CT (chest, abdomen, pelvis)[4]	**8cc**	✓			✓			✓		✓					✓		
	Colonoscopy[5]	**8cc**	✓			✓										✓		
Intermittent assessments	VES-13 questionnaire[6] (65≥ years at registration)	**5**	✓													✓		
	Cognitive assessment[6]	**6**	✓					✓								✓		
	International Physical Activity Questionnaire	**8**						✓								✓		
	HRQoL[7]			✓	✓	✓		✓	✓	✓	✓		✓		✓			
Blood tests	CEA test	**1cc, 7, 8cc**	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
	FBC, LFT, U&E & eGFR	**3**	✓	✓		✓		✓		✓		✓		✓		✓		
	C-Reactive Protein (CRP)	**3, 8**	✓			✓		✓										
	Fasting lipid profile	**3**	✓															
	Research Blood sample[8]		✓✓[9]	✓	✓	✓		✓	✓	✓	✓		✓		✓			
Other tests	Clinical Examination		✓															
	Tumour sample to be stored in bio-bank [8,10]	**2**	✓															
	Urine sample to be stored in biobank[10] **(selected sites)**	**2a**	✓	✓	✓													
	Survival Status[11]																✓	✓
	Tumour biopsy at recurrence[10,12]																	

[1a] Registration assessments include: eligibility, co-enrolment (*if applicable), blood pressure, height, weight, blood results, concomitant medication and comorbidities. This should coincide with the POLEM end of chemotherapy treatment visit.

[1b] POLEM end of treatment visit is +28 days (+7) from end of adjuvant chemotherapy and should coincide with Add-Aspirin registration. Includes clinical examination.

[2] End of run-in assessments include: symptoms and toxicity, adherence, blood pressure. This should coincide with the POLEM 6 month visit.

[3] Follow-up assessments include: symptoms and toxicity, adherence, blood pressure, weight, concomitant medication. Will require on-site assessments. POLEM visits allow a window of flexibility, and can occur +/- 1 month in the first year, and +/-3months thereafter.

[4] Imaging examinations can be performed can be performed within +/- 6 months from scheduled assessment point. The Add-Aspirin prior to registration CT can be patient's baseline diagnostic scan. The month 60 CT is mandatory. Note that the imaging assessment schedule for participants in the Add-Aspirin – POLEM collaboration differs to the standard Add-Aspirin protocol.

[5] Colonoscopies can be performed within +/- 6months from scheduled assessment point. Note that the colonoscopy assessment schedule for the Add-Aspirin – POLEM collaboration differs to standard Add-Aspirin protocol.

[6] UK only

[7] To be assessed using the EORTC QLQ C-30 and the EuroQol EQ-5D-5L questionnaires.

[8] See POLEM laboratory manual for details. Research blood sample required at each POLEM visit.

[9] 2 x Research blood samples required at this time for both Add-Aspirin and POLEM

[10] Where participants have given their consent.

[11] Assessment of survival status can be done remotely by a phone call to the patient or General Practitioner by the site research nurse

[12] This can be done under either endoscopic or radiological guidance. Samples from the relapsed tumour will be used for the POLEM translational analyses. See laboratory manual for details. This is applicable only to subjects who provided consent for an optional research biopsy at the time of tumour recurrence. Requires coagulation with PT, PTT and INR.

5.B) Add-Aspirin – POLEM Collaboration Trial Assessment Schedule (Colorectal Cohort)
For Patients in the CONTROL Arm on 24 WEEKS of adjuvant chemotherapy (Capecitabine)

AA VISITS	MONTHS SINCE ADD-ASPIRIN RANDOMISATION	CRF NUMBER	PRIOR TO REGISTRATION	PRIOR TO RANDOMISATION (END OF RUN-IN PERIOD)	3M	6M	9M	12M	18M	24M	30M	36M	42M	48M	54M	60M	-	-
POLEM VISITS	**MONTHS SINCE START OF ADJUVANT CHEMOTHERAPY**		**END OF TREATMENT VISIT[1B]**	**9M**	**12M**		**18M**	**24M[3B]**		**30M[3B]**		**36M[3B]**		**48M[3B]**		**60M[3B]**		**72M[3B]**	**84M**
Main assessments	AA Registration assessments[1a]	**1cc, 3, 4, 16***	✓															
	AA End of run-in assessment[2]	**7**		✓														
	Follow up assessments[3]	**8, 8cc**			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Imaging and procedures	CT (chest, abdomen, pelvis)[4]	**8cc**	✓		✓			✓		✓						✓		
	Colonoscopy [5]	**8cc**	✓		✓											✓		
Intermittent assessments	VES-13 questionnaire[6] (65≥ years at registration)	**5**	✓													✓		
	Cognitive assessment[6]	**6**	✓					✓								✓		
	International Physical Activity Questionnaire	**8**						✓								✓		
	HRQoL[7]			✓	✓		✓		✓	✓	✓		✓		✓			
Blood tests	CEA test	**1cc, 7, 8cc**	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
	FBC, LFT, U&E & eGFR	**3**	✓	✓		✓		✓		✓		✓		✓		✓		
	C-Reactive Protein (CRP)	**3, 8**	✓			✓		✓										
	Fasting lipid profile	**3**	✓															
	Research Blood sample [8,10]		✓✓[9]	✓	✓		✓		✓	✓	✓		✓		✓			
Other tests	Clinical Examination		✓															
	Tumour sample to be stored in bio-bank[8,10]	**2**	✓															
	Urine sample to be stored in biobank[10] **(selected sites)**	**2a**	✓	✓	✓													
	Survival Status[11]																✓	✓
	Tumour biopsy at recurrence[10] [12]																	

[1a] Registration assessments include: eligibility, co-enrolment (*if applicable), blood pressure, height, weight, blood results, concomitant medication and comorbidities. This should coincide with the POLEM end of chemotherapy treatment visit.

[1b] POLEM end of treatment visit is +28 days (+7) from end of adjuvant chemotherapy and should coincide with Add-Aspirin registration. Includes clinical examination.

[2] End of run-in assessments include: symptoms and toxicity, adherence, blood pressure. This should coincide with the POLEM 9month visit.

[3] Follow-up assessments include: symptoms and toxicity, adherence, blood pressure, weight, concomitant medication. Will require on-site assessments.

[3b] POLEM visits allow a window of flexibility, and can occur +/- 1 month in the first year, and +/-3months thereafter. Therefore, where indicated, POLEM visits can fall on either Add-Aspirin scheduled visit.

[4] Imaging examinations can be performed can be performed within +/- 6 months from scheduled assessment point. The Add-Aspirin prior to registration CT can be patient's baseline diagnostic scan. The month 60 CT is mandatory. Note that the imaging assessment schedule for participants in the Add-Aspirin – POLEM collaboration differs to the standard Add-Aspirin protocol.

[5] Colonoscopies can be performed within +/- 6months from scheduled assessment point. Note that the colonoscopy assessment schedule for the Add-Aspirin – POLEM collaboration differs to standard Add-Aspirin protocol.

[6] UK only

[7] To be assessed using the EORTC QLQ C-30 and the EuroQol EQ-5D-5L questionnaires.

[8] See POLEM laboratory manual for details. Research blood sample required at each POLEM visit.

[9] 2 x Research blood samples required at this time for both Add-Aspirin and POLEM

[10] Where participants have given their consent.

[11] Assessment of survival status can be done remotely by a phone call to the patient or General Practitioner by the site research nurse

[12] This can be done under either endoscopic or radiological guidance. Samples from the relapsed tumour will be used for the POLEM translational analyses. See laboratory manual for details. This is applicable only to subjects who provided consent for an optional research biopsy at the time of tumour recurrence. Requires coagulation with PT, PTT and INR.

5.C) Add-Aspirin – POLEM Collaboration Trial Assessment Schedule (Colorectal Cohort) Investigational (AVELUMAB) Arm & 12 WEEKS of adjuvant chemotherapy

AA VISITS	MONTHS SINCE ADD-ASPIRIN RANDOMISATION	CRF NUMBER	PRIOR TO REGISTRATION	PRIOR TO RANDOMISATION (END OF RUN-IN PERIOD)	3M	6M	9M	12M	18M	24M	30M	36M	42M	48M	54M	60M	-
POLEM VISITS	MONTHS SINCE START OF ADJUVANT CHEMOTHERAPY		END OF TREATMENT VISIT[1b]	12M		18M		24M	30M	36M		48M		60M		72M	84M
Main assessments	Registration assessments[1a]	**1cc, 3, 4, 16***	✓														
	End of run-in assessment[2]	**7**		✓													
	Follow-up assessments[3]	**8, 8cc**			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Imaging and procedures	CT (chest, abdomen, pelvis)[4]	**8cc**	✓	✓				✓		✓						✓	
	Colonoscopy[5]	**8cc**	✓	✓												✓	
Intermittent assessments	VES-13 questionnaire[6] (65≥ years at registration)	**5**	✓													✓	
	Cognitive assessment[6]	**6**	✓					✓								✓	
	International Physical Activity Questionnaire	**8**						✓								✓	
	HRQoL[7]			✓		✓		✓	✓	✓		✓		✓			
Blood tests	CEA test	**1cc, 7, 8cc**	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
	FBC, LFT, U&E & eGFR[8]	**3**	✓	✓		✓		✓		✓		✓		✓		✓	
	C-Reactive Protein (CRP)	**3, 8**	✓			✓		✓									
	Thyroid function test (TFTs)[9]		✓	✓	✓	✓		✓	✓	✓		✓		✓			
	Fasting lipid profile	**3**	✓														
	Research Blood sample[10]		✓✓[10b]	✓		✓		✓	✓	✓		✓		✓			
Other tests	Pregnancy Test[11]		✓														
	Clinical Examination		✓														
	ECOG Performance Status			✓		✓		✓	✓	✓		✓		✓			
	Tumour sample to be stored in bio-bank[12]	**2**	✓														
	Urine sample to be stored in biobank[12] **(selected sites)**	**2a**	✓	✓	✓												
	Survival Status[13]															✓	✓
	Tumour biopsy[12,14]																

[1a] Registration assessments include: eligibility, co-enrolment (if applicable), blood pressure, height, weight, blood results, concomitant medication and comorbidities. This should coincide with the POLEM end of treatment visit.

[1b] POLEM end of treatment visit is +28 days (+7) from end of Avelumab treatment and should coincide with Add-Aspirin registration. Includes AE assessment, clinical examination and pregnancy test

[2] End of run-in assessments include: symptoms and toxicity, adherence, blood pressure. This should coincide with the POLEM 12month visit if had 12 weeks of adjuvant chemotherapy.

[3] Follow up assessments include: symptoms and toxicity, adherence, blood pressure, weight, concomitant medication, AE assessments. Will require on-site assessments.

[4] Imaging examinations can be performed can be performed within +/- 6 months from scheduled assessment point. The Add-Aspirin prior to registration CT can be patient's baseline diagnostic scan. Month 60 CT is mandatory. Note that the imaging assessment schedule for Add-Aspirin – POLEM collaboration differs to the standard colorectal Add-Aspirin protocol.

[5] Colonoscopies can be performed within +/- 6 months from scheduled assessment point. Note that the colonoscopy assessment schedule for Add-Aspirin – POLEM collaboration differs to the standard colorectal Add-Aspirin protocol.

[6] UK only

[7] To be assessed using the EORTC QLQ C-30 and the EuroQol EQ-5D-5L questionnaires.

[8] FBC includes Hb, WBC, ANC, Platelets. Biochemistry (U&Es and LFTs) also includes AST, ALT, GGT, ALP, bilirubin, LDH, urea, creatinine, uric acid, total protein, serum albumin, glucose, sodium, potassium, magnesium, calcium, chloride, phosphate, amylase, lipase (applicable only to subjects in the investigational arm of POLEM)

[9] Includes TSH, free T3 and free T4 (applicable only to subjects in the investigational arm).

[10] See POLEM laboratory manual for details. Research blood sample required at each POLEM visit.

[10b] 2 x Research blood samples required at this time for both Add-Aspirin and POLEM

[11] To be done with serum or urine HCG

[12] Where participants have given their consent.

[13] Assessment of survival status can be done remotely by a phone call to the patient or General Practitioner by the site research nurse

[14] This can be done under either endoscopic or radiological guidance. Samples from the relapsed tumour will be used for the POLEM translational analyses. See laboratory manual for details. This is applicable only to subjects who provided consent for an optional research biopsy at the time of tumour recurrence. Requires coagulation with PT, PTT and INR.

5.D) Add-Aspirin – POLEM Collaboration Trial Assessment Schedule (Colorectal Cohort) Investigational (AVELUMAB) Arm & 24 WEEKS of adjuvant chemotherapy

AA VISITS	MONTHS SINCE ADD-ASPIRIN RANDOMISATION	CRF NUMBER	PRIOR TO REGISTRATION	PRIOR TO RANDOMISATION (END OF RUN-IN PERIOD)	3M	6M	9M	12M	18M	24M	30M	36M	42M	48M	54M	60M	-
POLEM VISITS	**MONTHS SINCE START OF ADJUVANT CHEMOTHERAPY**		**END OF TREATMENT VISIT[1B] = 12M**	**15M (90DAYS FROM LAST AVELUMAB)**	**18M**		**24M**	**30M[3B]**		**36M[3B]**	**48M[3B]**		**60M[3B]**		**72M[3B]**		**84M**
Main assessments	Registration assessments[1a]	**1cc, 3, 4, 16***	✓														
	End of run-in assessment[2]	**7**		✓													
	Follow-up assessments[3]	**8, 8cc**		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Imaging and procedures	CT (chest, abdomen, pelvis)[4]	**8cc**	✓				✓			✓						✓	
	Colonoscopy [5]	**8cc**	✓													✓	
Intermittent assessments	VES-13 questionnaire[6] (65≥ years at registration)	**5**	✓													✓	
	Cognitive assessment[6]	**6**	✓					✓								✓	
	International Physical Activity Questionnaire	**8**						✓								✓	
	HRQoL[7]				✓		✓		✓	✓		✓		✓			
Blood tests	CEA test	**1cc, 7, 8cc**	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
	FBC, LFT, U&E & eGFR[8]	**3**	✓	✓	✓	✓	✓	✓		✓		✓		✓		✓	
	C-Reactive Protein (CRP)	**3, 8**	✓			✓		✓									
	Thyroid function test (TFTs)[9]		✓	✓	✓		✓		✓	✓		✓		✓			
	Fasting lipid profile	**3**	✓														
	Research Blood sample[10]		✓✓[10b]		✓		✓		✓	✓		✓		✓			
Other tests	Pregnancy Test[11]		✓														
	Clinical Examination		✓														
	ECOG Performance Status				✓		✓		✓	✓		✓		✓			
	Tumour sample to be stored in bio-bank[11]	**2**	✓														
	Urine sample to be stored in biobank[12] **(selected sites)**	**2a**	✓	✓	✓												
	Survival Status[13]															✓	✓
	Tumour biopsy [12,14]																

[1a] Registration assessments include: eligibility, co-enrolment (if applicable), blood pressure, height, weight, blood results, concomitant medication and comorbidities. This should coincide with the POLEM end of treatment visit.

[1b] POLEM end of treatment visit is +28 days (+7) from end of Avelumab treatment and should coincide with Add-Aspirin registration. Includes AE assessment, clinical examination and pregnancy test

[2] End of run-in assessments include: symptoms and toxicity, adherence, blood pressure. This should coincide with the POLEM 48 week visit if had 12 weeks of adjuvant chemotherapy.

[3] Follow up assessments include: symptoms and toxicity, adherence, blood pressure, weight, concomitant medication, POLEM AE assessments. Will require on-site assessments.

[3b] To ensure POLEM and Add-Aspirin visits coincide, in patients who have had 24 weeks of adjuvant chemotherapy, 96 week POLEM visit will occur at 18month Add-Aspirin visit (rather than an extra visit at 15months post randomisation to Add-Aspirin).

[4] Imaging examinations can be performed can be performed within +/- 6 months from scheduled assessment point. The Add-Aspirin prior to registration CT is equivalent to the POLEM 12months scan. Month 60 CT is mandatory. Note that imaging assessment schedule for Add-Aspirin – POLEM collaboration differs to standard Add-Aspirin protocol.

[5] Colonoscopies can be performed within +/- 6 months from scheduled assessment point. Note that the colonoscopy assessment schedule for the Add-Aspirin – POLEM collaboration differs to the standard colorectal Add-Aspirin protocol.

[6] UK only

[7] To be assessed using the EORTC QLQ C-30 and the EuroQol EQ-5D-5L questionnaires.

[8] FBC includes Hb, WBC, ANC, Platelets. Biochemistry (U&Es and LFTs) for POLEM also includes AST, ALT, GGT, ALP, bilirubin, LDH, urea, creatinine, uric acid, total protein, serum albumin, glucose, sodium, potassium, magnesium, calcium, chloride, phosphate, amylase, lipase (applicable only to subjects in the investigational arm of POLEM for first 2 years).

[9] Includes TSH, free T3 and free T4 (applicable only to subjects in the investigational arm).

[10] See POLEM laboratory manual for details Research blood sample required at each POLEM visit.

[10b] 2 x Research blood samples required at this time for both Add-Aspirin and POLEM

[11] To be done with serum or urine HCG

[12] Where participants have given their consent.

[13] Assessment of survival status can be done remotely by a phone call to the patient or General Practitioner by the site research nurse

[14] This can be done under either endoscopic or radiological guidance. Samples from the relapsed tumour will be used for the POLEM translational analyses. See laboratory manual for details. This is applicable only to subjects who provided consent for an optional research biopsy at the time of tumour recurrence. Requires coagulation with PT, PTT and INR.

In a scenario where a patient finishes adjuvant chemotherapy earlier or later than expected (+/- 6 weeks), for example due to toxicity, follow protocol to the nearest expected week. For example, if a patient stops chemotherapy after 8 weeks instead of 12 weeks of treatment, assume patient has completed 12 weeks, and follow protocol appropriately

6 FOLLOW UP REQUIREMENTS:

Follow up in POLEM has been aligned with Add-Aspirin, with the same assessment requirements with the exception of the following extra investigations listed below. These assessments are required in all patients who have undergone POLEM treatment, regardless of whether or not they subsequently enter Add-Aspirin.

1. Thyroid function test including TSH, free T3 and free T4 (only in the investigational/Avelumab arm)
2. Additional biochemistry test, including AST, ALT, GGT, ALK-P, total bilirubin, LDH, urea, creatinine, uric acid, total protein, serum albumin, glucose, sodium, potassium, magnesium, calcium, phosphate, chloride, amylase, lipase (only in the investigational arm and for the first 2 years of POLEM follow up)
3. One extra CT requirement
4. One extra colonoscopy
5. Documentation of ECOG performance status with each visit
6. Collection of QoL data using the EORTC QLQ C-30 and the EuroQoL EQ-5D-5L questionnaires
7. Collection of research blood samples at each follow up visit (see POLEM laboratory manual for details). These specimens should be collected only after the patient has provided consent. Where possible, research blood samples should occur at the same time as other blood tests in order to avoid the need for additional venesection.
8. Optional tumour biopsy at progression

Those patients who have entered POLEM prior to Add-Aspirin will need follow up for 7 years from the start of adjuvant chemotherapy. POLEM assessments occur every 3 months (+/-1 month) during year 1, every 6 months (+/-3 months) during year 2 and 3, and every 12 months (+/- 3 months) during year 4 to 7 (as per Appendix XIV, Section 6). This window of assessments allow both the POLEM schedule and Add-Aspirin schedule to align. Follow-up for the assessment of the survival status can be done remotely at year 6 (+/- 3 months) and 7 (+/- 3 months) (i.e., phone call by the site research nurse to the patient of General Practitioner).

Additional investigation may be performed as clinically indicated especially in the presence of a suspicion of tumour recurrence or abnormal test results. In particular, thyroid function tests including TSH, free T3 and free T4 should be performed more frequently than above recommended if more intensive follow-up for avelumab-induced hypothyroidism or hyperthyroidism is clinically indicated.

6A) Assessments and follow-up after disease relapse

If documented tumour recurrence occurs during follow-up no additional visits are required.

Research blood samples will be collected. Furthermore, if the recurrent tumour is amenable to sampling, a research biopsy will be considered in selected centres if appropriate consent had been taken for this additional procedure at baseline. This biopsy could be under radiological (either US or CT scan) or endoscopic guidance (see the laboratory manual for more details). Subjects will need to have pre-biopsy blood tests including haematology, biochemistry and coagulation as indicated in the Assessment Schedule above (Appendix XIV, Section 5).

If a tumour biopsy is required, sites should discuss the recommended duration with which to withhold Add-Aspirin trial medication with the interventional radiologist or endoscopist. Subjects

not on Add-Aspirin, and on POLEM follow up alone, are permitted use of anticoagulants. Generally it is recommended to stop use of antocoagulation 24-48 hours prior to the biopsy and recommencing 24-48 hours after the procedure on recommendation of the interventional radiologist or endoscopist. Subjects who are on oral coumadin derivatives (i.e., warfarin) will be strongly encouraged to switch to subcutaneous anticoagulants (i.e., low molecular weight heparin) at study entry. However, if this is not possible due to clinical reasons or subject preference, the coagulation parameters will be carefully monitored by the treating physician and the interventional radiologist or endoscopist performing the procedure.

Any other POLEM study-related procedure should be discontinued upon tumour recurrence and subjects will be treated and followed up as per standard of care. Nevertheless, the following information should be still collected for all subjects:

- Details of any post-recurrence therapies should be recorded.
- Follow up for survival should continue every 6 months until death or trial closure. This may occur by telephone contact or via the patient's general practitioner

Participants on the Add-Aspirin trial can continue trial medication upon recurrence, as per Section 5.8 of the main Add-Aspirin Protocol.

6B) Withdrawal Criteria for POLEM Follow-Up

Patients have the right to withdraw fully or partially from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution. Patients who are withdrawn from the study will not be replaced.

Withdrawal of full consent for a study means that the patient does not wish to receive further investigational treatment and does not wish to or is unable to continue further study participation. Any patient may withdraw full consent to participate in the study at any time during the study. The investigator will discuss with the patient the most appropriate way to withdraw to maintain the patient's care. In this case, the patient's data already collected up to the point of withdrawal will still be included in the analysis of data, and the patient censored from that point onwards, unless the patient has explicitly requested that none of the data collected should be used for analysis. If the patient consents, SAE data will continue to be collected for 90 days after the last avelumab treatment received, even if the patient has withdrawn from the study.
Withdrawal of partial consent means that the patient does not wish to take investigational product any longer but is still willing to collaborate in providing further data by continuing on study (e.g., participate in all subsequent study visits or procedures).

Patients may decline to continue receiving study treatment at any time during the study. Such patients, as well as those who have stopped receiving the study treatment for other reasons, such as principal investigator, chief investigator or sponsor concern, should also continue the schedule of study observations.

Reasons for removal of patients from the study may include:

- withdrawal of consent.
- administrative decision by the investigator, chief investigator or sponsor.
- pregnancy.
- ineligibility
- significant protocol deviation.
- patient non-compliance.

- AE

For participants who wish to withdraw from Add-Aspirin follow-up, please refer to section 6.10 of the main Add-Aspirin Protocol for more guidance

6C) Storage and analysis of samples

Tumour biopsies

At baseline tumour samples will be obtained from the resection specimen. Cores will be placed in formalin and processed for formalin-fixed, paraffin-embedded blocks. In participants found to have dMMR tumours (following a local IHC test as per NICE guidance) resection samples will be sent to the Royal Marsden NHS Foundation Trust (see POLEM laboratory manual for further details).

Tumour samples from resection specimens will be used for the translational research programme (see laboratory manual for more details) if the patient enters the study. Any tumour samples from not used in POLEM translational studies, will be sent to the Add-Aspirin biobanks for use in future Add-Aspirin translational research.

In selected participating centres, tumour samples from the recurrent tumour may also be obtained, if feasible and appropriate according to the judgement of the local investigator, from subjects who have consented for an optional biopsy. At least one core of tissue is required, and should be placed in formalin and processed for FFPE. However, if clinically appropriate and technically feasible, up to 4 cores of tissue should be obtained. Appropriately labelled tissue blocks should be sent to the Royal Marsden NHS Foundation Trust when requested. These samples will be used for the translational research programme (see laboratory manual for more details).

POLEM Blood Samples

All patients will be asked to consent to have a research blood sample (i.e., 35ml) collected for the purpose of banking whole blood, serum and plasma. These will be collected at each follow-up visit (as well as during treatment visits whilst at POLEM centres).

These specimens should be collected only after the patient has provided consent. Where possible, research blood samples should occur at the same time as other blood tests in order to avoid the need for additional venesection. Please refer to the laboratory manual for details regarding collection, handling and storage of these samples. With exception to those samples that will require immediate couriering (details of which are outlined in the laboratory manual) the samples should be stored at the site until requested by the CTU at the Royal Marsden NHS Foundation Trust who will arrange collection of the samples for analysis.

POLEM Sample Labelling, Storage and Destruction

In order to protect patient identity, blood and stool samples and tumour blocks should not be labelled with any information that may lead to the direct identification of the patient concerned, including patient name, date of birth, or National Health Service (NHS) or hospital number. Instead blood samples and tumour blocks should be labelled with the study name, the patient's study number (registration number at time of initial registration; randomisation number in patients subsequently enrolled), initials, date of sample collection and visit designation (baseline, cycle number, end of study visit or follow up visit). On biopsy tissue samples, the label should also include the anatomical location of the biopsied lesion.

Centres should also keep a record of blood and tissue samples collected that includes the same information. In addition, the date of transfer of samples to the lead centre should be recorded in the CRF.
Prior to transfer to the RMH CTU, centres should ensure that blood and tumour samples are appropriately stored. Blood samples should be stored at -80°C (or -20°C if you do not have access to a -80°C freezer).

For patients consented for biopsy of relapsed tissue some centres maybe be able to obtain fresh frozen tissue this must be stored at -80°C. Paraffin-embedded tissue blocks should be stored at room temperature away from light. Blood and tissue samples will be stored indefinitely. However, the patient retains the right to have the sample material returned to their hospital pathology department or destroyed at any time by contacting the principal investigator at the site at which they were registered for the study. The site principal investigator will then be responsible for contacting the sponsor via the chief investigator to arrange for the return or destruction of the samples.

The sponsor will be the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible, via the chief investigator, for the destruction of the sample(s) at the request of the research patient through the site principal investigator or at the end of the storage period. The site principal investigator will provide the chief investigator with the required patient study numbers so that any unused blood and tissue samples can be located and destroyed.

6C) POLEM End of Trial

The end of the study is defined as such time as the last patient has had their last visit, or when adequate follow up has occurred for all the study end points to be assessed and reported (including overall survival which will require patients to be followed up until 7 years from the start of adjuvant chemotherapy, death or loss to follow-up), whichever is sooner. At this point, the 'end of trial notification' will be submitted to the relevant regulatory authorities including the UK Medicine and Healthcare products Regulatory Agency (MHRA) and the relevant REC Committee.

It is likely that Add-Aspirin end of trial will occur earlier than POLEM end of trial, however the collaboration will remain open until both colorectal trials complete.

7 DATA COLLECTION (CRFS) PROCESS FOR SITES

Add-Aspirin centres not participating in POLEM will record POLEM follow up data on POLEM-specific paper CRFs, and send these to the central POLEM CTU team (E-mail: gi.trials@rmh.nhs.uk; Fax: 0208 661 3750) for entry onto the POLEM database.

For centres participating fully in POLEM, electronic data capture should proceed in accordance with the POLEM protocol.

For all centres, Add-Aspirin follow-up data collection should proceed in accordance with the main protocol, with Add-Aspirin-specific paper CRFs sent to the MRC CTU team.

8 POLEM TRIAL MEDICATION

Treatment on the investigational arm with Avelumab will only be administered at POLEM specific centres, once every 2 weeks for 24 weeks (i.e. 12 treatment cycles) after completion 12 or 24 weeks of standard fluoropyrimidine-based adjuvant chemotherapy.

Patients randomised to the control arm can be transferred back to their original Add-Aspirin cente, following adjuvant chemotherapy, for registration and ongoing randomisation into Add-Aspirin.

8A). Legal status of the investigational medicinal product (IMP)

Avelumab is not yet licensed within Europe although licensing is in progress in Merkel Cell carcinoma. The trial is being carried out under a Clinical Trial Authorisation (CTA). The drug is therefore only to be used by the named investigators, for the patients specified in this protocol, and within the trial, and approved POLEM treating centres.

8B). Concomitant medication on POLEM

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care. Use of steroids is allowed to manage treatment-related adverse events as clinically indicated and recommended below. Should this occur, treatment within Add-Aspirin may need to be held (as long term corticosteroids use in not permitted in the Add-Aspirin trial), but will require discussion with the MRC CTU at UCL.

Concomitant treatment considered necessary for the patient's wellbeing may be given at discretion of the treating physician. However, should any of these treatments fall into the Add-Aspirin list of non-permitted medication (see appendix 1), please discuss with the MRC CTU at UCL. Concomitant medications and treatments, including herbal supplements, will be recorded from 28 days prior to the start of study treatments and up to 90 days after the last dose of Avelumab treatment. All concomitant medications should be recorded in both the Add-Aspirin and POLEM CRFs including supportive care drugs (e.g., antiemetic treatment and prophylaxis), and the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (e.g., transfusions). Concurrent anticancer therapy with agents other than study treatments is not allowed. Medications intended solely for supportive care (see below) are allowed.

Recommended medications to treat immune-related events are reported below in Section 8D.

8C). Trial restrictions

During the follow-up phase of this trial patients are prohibited from receiving the following:

- live vaccines for 3 months after the last dose of chemotherapy in patients who have been randomised to the control arm
- live vaccines for 3 months after the last dose of avelumab in patients who have been randomised to the investigational arm.

8D) Management of Immune-mediated Adverse Reactions:

Gastrointestinal irAEs		
Severity of Diarrhoea/Colitis (NCI-CTCAE v4)	**Initial Management**	**Follow-Up Management**
Grade 1 Diarrhea: < 4 stools/day over baseline Colitis: asymptomatic	Continue Avelumab therapy Symptomatic treatment (e.g. loperamide)	Close monitoring for worsening symptoms Educate subject to report worsening immediately. If worsens: Treat as Grade 2, 3 or 4.
Grade 2 Diarrhea: 4 to 6 stools per day over baseline; IV fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Withhold Avelumab therapy. Symptomatic treatment.	If improves to Grade ≤ 1: Resume Avelumab therapy. If persists > 5-7 days or recurs: Treat as Grade 3 or 4. Contact treating POLEM centre if follow-up at Add-Aspirin site.
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 h; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Withhold Avelumab for Grade 3. Permanently discontinue Avelumab for Grade 4 or recurrent Grade 3. 1.0 to 2.0 mg/kg/day prednisone IV or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider lower endoscopy	If improves: Continue steroids until Grade ≤ 1, then taper over at least 1 month; resume AvelumabAvelumab therapy following steroids taper (for initial Grade 3). If worsens, persists > 3 to 5 days, or recurs after improvement: Add infliximab 5mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis. Contact treating POLEM centre if follow-up at Add-Aspirin site.
Dermatological irAEs		
Grade of Rash (NCI-CTCAE v4)	**Initial Management**	**Follow-Up Management**
Grade 1 to 2 Covering ≤ 30% body surface area	Continue Avelumab therapy. Symptomatic therapy (for example, antihistamines, topical steroids).	If persists > 1 to 2 weeks or recurs: Withhold Avelumab therapy Consider skin biopsy Consider 0.5-1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume Avelumabtherapy following steroids taper. If worsens: Treat as Grade 3 to 4. Contact treating POLEM centre if follow-up at Add-Aspirin site.
Grade 3 to 4	Withhold	If improves to Grade ≤1:

Grade 3: Covering > 30% body surface area; Grade 4: Life threatening consequences	Avelumab for Grade 3. Permanently discontinue for Grade 4 or recurrent Grade 3. Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections	Taper steroids over at least 1 month; resume AvelumabAvelumab therapy following steroids taper (for initial Grade 3). Contact treating POLEM centre if follow-up at Add-Aspirin site.
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4)	**Initial Management**	**Follow-Up Management**
Grade 1 Radiographic changes only	Consider withholding AAvelumab therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-assess at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4.
Grade 2 Mild to moderate new symptoms	Withhold Avelumab therapy Pulmonary and Infectious Disease consults Monitor symptoms daily; consider hospitalization 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider bronchoscopy, lung Biopsy.	Re-assess every 1 to 3 days If improves: When symptoms return to Grade ≤ 1, taper steroids over at least 1 month, and then resume Avelumab therapy following steroids taper. If not improving after 2 weeks or worsening: Treat as Grade 3 to 4. Contact treating POLEM centre if follow-up at Add-Aspirin site.
Grade 3 to 4 Grade 3: Severe new symptoms; New/worsening hypoxia; Grade 4: Life-threatening	Permanently discontinue Avelumab therapy. Hospitalize. Pulmonary and Infectious Disease consults. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider bronchoscopy, lung biopsy	If improves to Grade ≤ 1: Taper steroids over at least 1 month If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil) Contact treating POLEM centre if follow-up at Add-Aspirin site.
Hepatic ir AEs		
Grade of Liver Test Elevation (NCI-CTCAE v4)	**Initial Management**	**Follow-Up Management**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and/or total bilirubin > ULN to 1.5 x ULN	Continue Avelumab therapy	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4.
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or total bilirubin > 1.5 to ≤ 3 x ULN	Withhold Avelumab therapy Increase frequency of monitoring to every 3 days	If returns to Grade ≤ 1: Resume routine monitoring; resume Avelumab therapy. If elevation persists > 5 to 7 days or worsens:

		Treat as Grade 3 to 4. Contact treating POLEM centre if follow-up at Add-Aspirin site.
Grade 3 to 4 AST or ALT > 5 x ULN and/or total bilirubin > 3 x ULN	Permanently discontinue Avelumab therapy. Increase frequency of monitoring to every 1 to days 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consult gastroenterologist/ hepatologist. Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted.	If returns to Grade ≤ 1: Taper steroids over at least 1 Month. If does not improve in > 3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily. If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines. Contact treating POLEM centre if follow-up at Add-Aspirin site.
Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v4)	**Initial Management**	**Follow-Up Management**
Grade 1 Creatinine increased > ULN to 1.5 x ULN	Continue Avelumab therapy.	Continue renal function monitoring. If worsens: Treat as Grade 2 to 3 or 4.
Grade 2 to 3 Creatinine increased > 1.5 and ≤ 6 x ULN	Withhold Avelumab therapy Increase frequency of monitoring to every 3 days. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider renal biopsy	If returns to Grade ≤1: Taper steroids over at least 1 month, and resume Avelumab therapy following steroids taper. If worsens: Treat as Grade 4. Contact treating POLEM centre if follow-up at Add-Aspirin site.
Grade 4 Creatinine increased > 6 x ULN	Permanently discontinue Avelumab therapy. Monitor creatinine daily 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider renal biopsy Nephrology consult	If returns to Grade ≤1: Taper steroids over at least 1 month. Contact treating POLEM centre if follow-up at Add-Aspirin site.
Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-Up Management**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin, CKMB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	Withhold Avelumab therapy. Hospitalise. In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish aetiology and rule-out immune mediated myocarditis. Guideline based supportive treatment as per cardiology	If symptoms improve and immune-mediated aetiology is ruled out, re-start Avelumab therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated aetiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis. Contact treating POLEM centre if

	consult.* Consider myocardial biopsy if recommended per cardiology consult	follow-up at Add-Aspirin site.
Immune-mediated myocarditis	Permanently discontinue Avelumab. Guideline based supportive treatment as appropriate as per cardiology consult.* 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections.	Once improving, taper steroids over at least 1 month. If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A). Contact treating POLEM centre if follow-up at Add-Aspirin site.
*Local guidelines, or eg. ESC or AHA guidelines ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001		
Endocrine irAEs		
Endocrine Disorder	**Initial Management**	**Follow-Up Management**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Continue Avelumab therapy. Endocrinology consult if needed. Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Continue hormone replacement/ suppression and monitoring of endocrine function as appropriate.
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Withhold Avelumab therapy. Consider hospitalisation. Endocrinology consult. Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Resume Avelumab once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/ suppression). Continue hormone replacement/ suppression and monitoring of endocrine function as appropriate. Contact treating POLEM centre if follow-up at Add-Aspirin site.
Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (i.e. subnormal serum FT4 with inappropriately low TSH and/ or low serum cortisol with inappropriately low ACTH) :	Resume Avelumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement). In addition, for hypophysitis with

	• Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/ IGF-1, PRL, testosterone in men, oestrogens in women) • Hormone replacement/ suppressive therapy as appropriate • Perform pituitary MRI and visual field examination as indicated If hypophysitis confirmed: • Continue Avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month • Withhold Avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/ or abnormal MRI. Consider hospitalisation. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. • Add prophylactic antibiotics for opportunistic infections.	abnormal MRI, resume Avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. Continue hormone replacement/ suppression therapy as appropriate. Contact treating POLEM centre if follow-up at Add-Aspirin site.
Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v4)	**Initial Management**	**Follow-Up Management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold Avelumab therapy pending clinical investigation.	If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting Avelumab therapy. If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold Avelumab therapy. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Speciality consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month and resume Avelumab therapy following steroids taper. Contact treating POLEM centre if follow-up at Add-Aspirin site.
Recurrence of same Grade 3 irAEs	Permanently discontinue Avelumab therapy. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections.	If improves to Grade ≤ 1: Taper steroids over at least 1 month. Contact treating POLEM centre if follow-up at Add-Aspirin site.

	Speciality consult as appropriate	
Grade 4	Permanently discontinue Avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent and/ or other immunosuppressant as needed. Add prophylactic antibiotics for opportunistic infections Speciality consult.	If improves to Grade ≤ 1: Taper steroids over at least 1 month Contact treating POLEM centre if follow-up at Add-Aspirin site.
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency. **Persistent Grade 2 or 3 irAE lasting 12 weeks or longer.**	Permanently discontinue Avelumab therapy. Speciality consult.	Contact treating POLEM centre if follow-up at Add-Aspirin site.

Abbreviations: ACTH=adrenocorticotropic hormone; ADL=activities of daily living; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BNP=B-type natriuretic peptide; CK-MB=creatine kinase MB; CT= computed tomography; FSH=follicle-stimulating hormone; GH=growth hormone; IGF-1=insulin-like growth factor 1; irAE=immune related adverse event; IV=intravenous; LH=luteinizing hormone; MRI=magnetic resonance imaging; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; PRL=prolactin;T4=thyroxine; TSH=thyroid stimulating hormone; ULN=upper limit of normal.

9 PHARMACOVIGILANCE

9A. Safety Reporting

Safety reporting within Add-Aspirin should proceed as per the main protocol.

Definitions for safety reporting, assessment of severity and assessment of causality within POLEM are as per Add-Aspirin (detailed in section 7 of the main protocol)

For the purpose of regulatory requirements, only the following events will be reported:

- AEs (or ARs) which occur in subjects randomised to the investigational arm from the first infusion of IMP until the end of follow-up
- SAEs (or SARs) which occur in subjects randomised to the investigational arm from the first infusion of IMP until 90 days after the last infusion of IMP.

AEs (and ARs) should be recorded in the medical notes and the appropriate section of the CRF and/or AE/AR log.

SAEs and SARs should be reported to the sponsor as detailed below

Patients who have received the investigational arm (Avelumab) of the POLEM trial:

- All SAEs occurring from the day of first infusion of IMP (Avelumab) until 90 days after the last infusion of IMP should be captured in the patients' medical records.
- Investigators should notify the MRC CTU at UCL (UK) and Gastrointestinal (GI) Unit Clinical Trial Office (CTO) at the Royal Marsden Hospital (RMH) by fax (Fax: +44 208 915 6731) of all SAEs occurring within 24 hours of discovery or notification of the event. Any change of condition or other follow-up information should be faxed to the CTO office within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

All adverse events considered to be serious and reactions (SARs and SUSARs):

- The Investigator must assess the causality of all serious events or reactions in relation to protocol treatment (either aspirin or Avelumab)
- If an SAE is considered possibly related to Avelumab AND the event occurs >90 days after the last dose of Avelumab, these SAEs will also be collected and reported to the RMH CTO (Fax: +44 208 915 6731) within 24 hours of discovery.
- If a serious event occurs and is considered possibly related to aspirin, the MRC CTU should be notified as specified in the main protocol.
- If there is any doubt as to the possible causality of the reaction, the SAE should be reported to both CTUs (MRC and RMH).
- the assessment of expectedness will be based upon Reference Safety Information of the investigator brochure (IB) for avelumab
- The sponsor / chief investigator will be responsible for expedited reporting of all SUSARs to the relevant authorities (including the UK Medicines and Healthcare products Regulatory Agency and the responsible main research ethics committee) no later than 7 calendar days after the sponsor has first knowledge of the minimum criteria for expedited reporting for SUSARs which are fatal or life threatening, or no later than 15 days for SUSARs which are non-fatal or non-life threatening. These will be simultaneously reported to Merck Serono. Other investigators will be informed of these events by a periodic line listing.

Information on the final description and evaluation of a SAR report may not be available within the required time frames for reporting. For regulatory purposes, initial expedited reports should be submitted within the time limits as soon as the minimum following criteria are met:

a) A suspected IMP
b) An identifiable subject (e.g. trial subject code number),
c) An AE assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship,
d) An identifiable reporting source,

And, when available and applicable:

a) A unique clinical trial identification (EudraCT number or in case of non-European Community trials the sponsor's trial protocol code number)
b) A unique case identification (i.e. sponsor's case identification number).

In case of incomplete information at the time of initial reporting, all the appropriate information for an adequate analysis of causality should be actively sought from the reporter or other available sources. Further available relevant information should be reported as follow-up reports.

In certain cases, it may be appropriate to conduct follow-up of the long-term outcome of a reaction.

<u>For all SAEs the following attributed must be assigned by the investigator:</u>

1. AE diagnosis or syndrome(s) - according to NCI-CTCAE version 4.0 classification. If AE diagnosis is not yet known, then signs or symptoms should be reported.

2. Severity – graded according to NCI-CTCAE version 4.0

3. Event description – include full details in medical terms and case description

4. Dates of onset and resolution – if not yet resolved then follow-up reports will be required until the event is considered resolved or stable.

5. Relatedness to the IMP - assessed by means of the question: “Is there a reasonable possibility that the event may have been caused by the IMP?” The investigator should respond to this question with either “related”, “probably related” or “possibly related” for events which may be related to the IMP and are therefore SARs, and “probably unrelated” or “unrelated” for events which are not related to study treatment and are therefore only SAEs.

6. Expectedness - based upon the Reference Safety Information of the investigator brochure (IB) for Avelumab (i.e., section 6.2 of the IB).

7. Action taken - the investigator may additionally be asked to provide follow-up information, discharge summaries, and / or extracts from medical records or CRFs.

8. Outcome

The investigator is responsible for ensuring that all SAEs captured on the patients’ medical records (as specified above) are reported on the CRF.

SAEs or SARs which are considered to be expected will be reported in a periodic line listing. Merck

Serono will each receive copies of all SAEs and SARs as well as a copy of the annual Drug Safety Update Reports (DSURs).

All SAEs reported to the CTU office shall be evaluated and escalated as appropriate in accordance with the RM / ICR SOP for SAE reporting. The chief investigator is also responsible for all submissions of annual reports to the RM R&D Office (the sponsor), MHRA and Ethics as indicated in the SOP.

It will be left to the investigator's clinical judgment to determine whether an SAE is related and of sufficient severity to require the patient's removal from treatment or from the study. A patient may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable SAE If either of these situations arises, the patient should be strongly encouraged to undergo the end-of-study visit and be under medical supervision until symptoms cease or the condition becomes stable. If a patient is permanently withdrawn from the study because of a SAE, this information must be included in the initial or follow-up SAE Report Form as well as the end of study CRF.

For all deaths, available post-mortem reports and relevant medical reports should be faxed to the Trials Unit as soon as they are available.

Reporting of targeted events:

The following AEs are considered POLEM targeted events and should be reported to the RMH CTO (E-mail: gi.trials@rmh.nhs.uk; Fax: 0208 661 3750) on an SAE report form within 24 hours of discovery or notification of the event even if they do not otherwise fulfil criteria for seriousness:

- Myocardial infarction, cardiac failure and myocarditis
- Pneumonitis which is felt to be treatment-related
- Hepatic dysfunction or hepatitis which are felt to be treatment-related
- Enterocolitis which is felt to be IMP-related
- Endocrinopathy which is felt to be IMP-related
- Neuropathy which is felt to be IMP-related
- Nephritis which is felt to be IMP-related

9B) POLEM Notification of Death

All deaths will be reported to the sponsor irrespective of whether the death is related to disease progression, the IMP, or an unrelated event. Death which is secondary to progressive disease should be reported on a death CRF but is not considered an SAE.

In Add-Aspirin, events relating to a patient primary cancer (including death), or a diagnosis of a new cancer, are required to be reported on SAE forms, however these do not need to be submitted within 24 hours of the investigator being aware the event (see section 7 of the main Add-Aspirin protocol for further details).

9C). Pregnancy reporting:

The Investigator must make every effort to try and ensure that a clinical trial patient or a partner of a clinical trial patient does not become pregnant during the POLEM trial or for 12 months afterwards. This should be done as part of the consent process by explaining clearly to the patient the potential dangers of becoming pregnant and also providing each patient with information about appropriate medically approved contraception. Two forms of medically approved contraception should be used, such as:

• oral contraceptives and condom;
• intra-uterine device (IUD) and condom;
• diaphragms with spermicidal gel and condom.

Contraceptives should be used from the time the patient joins the trial, throughout the trial and for 6 months after completing standard adjuvant chemotherapy or 30 days after the last infusion of Avelumab. It should be explained to the patient that if his partner is pregnant or breast-feeding when he enters the trial, the patient should use barrier method contraception (condom plus spermicidal gel) to prevent the unborn baby or the baby being exposed to chemotherapy or the IMP. The Investigator must ensure that all patients are aware at the start of the study of the importance of reporting all pregnancies (in themselves and their partners) that occur whilst being treated with the IMP and occurring up to 12 months after the last IMP administration.

If a trial participant or a trial participant's partner does become pregnant during treatment with the IMP or within 12 months of last IMP administration, it must be reported to the Chief Investigator and the Sponsor within 1 day of the site staff becoming aware of it using the Pregnancy Notification Form (and similarly Add-Aspirin's Notable Event form).

Participants who become pregnant must be discontinued from trial treatment immediately. It is the Investigator's responsibility to obtain consent for follow-up from the patient or patient's partner. The Sponsor will follow-up all pregnancies for the pregnancy outcome via the Investigator and document on the pregnancy form.

The Investigator should offer counselling to the participant and/or the partner, and discuss the risks of continuing with the pregnancy and the possible effects on the foetus. With appropriate consent, monitoring of the participant and/or the partner and the baby should continue until the conclusion of the pregnancy. Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the serious criteria, this would be considered an SAE and reported as such.

10 POLEM STUDY SUMMARY

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
Study trial	Avelumab plus fluoropyrimidine-based chemotherapy as adjuvant treatment for stage III dMMR or POLE exonuclease domain mutant colon cancer: A phase III open label randomised study.
Study number and acronym	CCR4673-POLEM
EudraCT #	2017000370-10
NRES No.	18/LO/0165
Planned number of patients	402 patients will be enrolled
Planned treatment duration per subject	Patients will be randomised in a 1:1 ratio to receive standard 12 or 24 weeks of fluoropyrimidine-based adjuvant chemotherapy (i.e., either 4 cycles of CAPOX or 8 cycles of single agent Capecitabine based on local investigator's decision) or fluoropyrimidine based chemotherapy followed by 24 weeks of Avelumab.
Study Objective	To demonstrate that administering Avelumab after standard adjuvant fluoropyrimidine-based chemotherapy improves the rate of 3-year disease free survival (DFS) compared with standard fluoropyrimidine-based adjuvant chemotherapy alone in stage III dMMR or POLE exonuclease domain mutant colon cancer
Primary Outcome Measure	3-year DFS - defined as the proportion of subjects who are alive and free of disease 3 years after randomisation
Secondary Objectives and Outcome Measures	1. To evaluate overall survival (OS) at 5 and 7 years by treatment arm 2. To evaluate survival outcomes (including DFS and OS) by predefined clinical, pathological and molecular factors - Subgroups analyses will be performed by POLE status, MMR status, age, gender, tumour location, type of adjuvant chemotherapy and TN stage 3. The safety profile/toxicity of the investigational treatment arm. 4. Health-related quality of life (HRQoL) assessed using the EORTC QLQ C-30 and the EuroQol EQ-5D-5L questionnaires 5. The cost effectiveness of adjuvant treatment by treatment arm assessed by Quality Adjusted Life Years (QALYs) and Health Resource Use
Exploratory / Translational	To evaluate predictive factors of clinical benefit and safety of Avelumab in tumour tissue and blood samples. Molecular studies will be performed on primary tumour tissues (resected specimens) and blood samples. If applicable, analyses will be extended to tumour tissues from the site of relapse.

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
Investigational therapy: product / dosing schedule / mode of administration	Avelumab will be administered once every 2 weeks intravenously at the dose of 10mg/kg body weight for 12 cycles.
Follow up duration	7 years (from the start of adjuvant chemotherapy)
Planned date for primary analysis:	End of September 2025
Planned date for analyses of follow-up phase data:	End of September 2029
Planned Trial Period	10 years
Sample size calculation	The primary endpoint is DFS at 3 years. The 3-year DFS rate in the control arm is expected to be about 75% (72). The experimental treatment (fluoropyrimidine-based chemotherapy followed by Avelumab) is expected to improve the 3-year DFS rate by 12% (to 87%), corresponding to a hazard ratio (HR) of 0.48. This effect size is justifiable since the population is highly enriched (with dMMR and POLE mutant patients) and secondly, a large effect size will also allow potential for cost-effectiveness of the experimental intervention. Therefore, a sample size of at least 171 per group (342 in total) is required (60 DFS events in total) to reject the null hypothesis of: H_0; HR =1 vs H_1: HR HR ≠ 1 with at least 80% power assuming a two sided 5% type I error. Assuming further a 15% dropout rate (loss to follow up rate) a total sample size of 402 will be required (201 per group in a 1:1 randomisation).
Co-Sponsors	
Funders	Merck Serono Financial support: Grant to support study Non-financial support: IMP and labelling

11.Contact Details:

Gastrointestinal Unit Clinical Trial Office at the Royal Marsden Hospital Sponsor contact:

- E-mail: gi.trials@rmh.nhs.uk
- Fax: 0208 661 3750