Research in Context Panel:

Evidence before this study: Preclinical data, epidemiological studies, and meta-analyses of randomised data from cardiovascular trials support the hypothesis that aspirin could be an effective adjuvant cancer therapy (Langley R, et al. Br J Cancer 2011;105(8):1107-13; Algra AM et al. Lancet Oncol 2012;13(5):518-27). Globally, several phase III studies are ongoing to assess this, though debate continues about the safety profile of aspirin particularly after radical therapy for gastrointestinal malignancies.

Added value of this study: The Add-Aspirin trial (encompassing 4 individually powered phase III studies in gastro-oesophageal, colorectal, prostate and breast cancer) is the largest of the ongoing trials and includes a pre-defined feasibility analysis to assess the acceptability of randomisation, tolerability and toxicity based on an open label run-in phase prior to double- blind randomisation. The data show that aspirin is well tolerated after radical cancer therapy, acceptable to patients, and there is no evidence to suggest there is increased toxicity in the gastro-oesophageal cohort over other tumour-specific cohorts.

Implications of all the available evidence: Aspirin is a low cost generic drug with the potential to have a large impact on cancer outcomes globally. Outcomes from gastro-oesophageal cancer remain poor and there is an imperative to complete recruitment to the ongoing trials as quickly as possible. The rationale and supporting evidence for evaluating aspirin as a potential anti-cancer therapy remains strong. More generally, a run-in approach may be useful in adjuvant (or prevention) studies for reducing the risk of non-adherence and participant attrition at a later date.

TITLE PAGE

Aspirin as an Adjuvant Treatment for Cancer: Feasibility Results from the Add-Aspirin Randomised Trial

Short Title: Add-Aspirin Trial: Feasibility & Early Toxicity

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ABSTRACT

Background: Pre-clinical, epidemiological and randomised data indicate aspirin prevents tumour development and metastases leading to reduced cancer mortality, particularly for gastro-oesophageal and colorectal cancer. Randomised trials evaluating aspirin use after primary radical therapy are ongoing. To address concerns about toxicity particularly bleeding after radical treatment for gastro-oesophageal cancer, a pre-planned feasibility analysis was incorporated into the ongoing Add-Aspirin trial.

Method: The Add-Aspirin protocol includes 4 phase III randomised-controlled trials evaluating the effect of aspirin on recurrence/survival after radical therapy in 4 tumour cohorts: gastro-oesophageal (GO), colorectal (CRC), breast and prostate. An open-label run-in phase (aspirin 100mg daily for 8 weeks) precedes double-blind randomisation (1:1:1 aspirin 300mg: aspirin 100mg: matched placebo). A pre-planned analysis of feasibility, including recruitment, adherence, and toxicity was performed. The trial is registered with the International Standard Randomised Controlled Trials Number registry (ISRCTN74358648), and remains open to recruitment.

Findings: After two years of recruitment (October 2015- October 2017), 3494 participants were registered on the trial (gastro-oesophageal 115, colorectal 950, breast 1675, prostate 754) with end of run-in data available for 2253. Adherence: 95% (2148/2253) took 6-7 tablets/week and 85% proceeded to randomisation, with rates consistent across tumour cohorts. 0·6% (14/2253) reported grade 3 toxicity during the run-in period, with no upper gastrointestinal bleeding (any grade) in the gastro-oesophageal cohort. The most frequent grade 1/2 toxicity overall was dyspepsia in 6.5% (146/2253).

Interpretation: Aspirin is well-tolerated after radical cancer therapy though marked differences in recruitment rates across the tumour cohorts within the Add-Aspirin trial were seen. Toxicity has been low and there is no evidence of a difference in adherence, acceptance of randomisation or toxicity between the cohorts. Aspirin offers a potential low cost and well tolerated therapy to improve gastrointestinal cancer outcomes.

Funding: Cancer Research UK, The National Institute for Health Research Health Technology Assessment Programme and The MRC Clinical Trials Unit at UCL.

Keywords: *aspirin; gastro-oesophageal cancer; colorectal cancer; toxicity*

Abbreviations used in this paper*: CI (confidence interval), CRT (chemoradiation), GI (gastrointestinal), GO (gastro-oesophageal), GCP (good clinical practice), HR (hazard ratio), NHS (National Health Service), NSAIDs (non-steroidal anti-inflammatory drugs), RCT (randomised controlled trial), RR (relative risk).*

Introduction

Globally, cancers arising from the oesophagus, stomach and colon account for approximately 20% of all cancer mortality (1). Mean five year survival rates from gastro-oesophageal cancer are particularly poor (15%) (2), attributed to the frequently advanced stage at presentation of the disease and the challenges of treatment (3). These factors are compounded in low and middle income countries by the lack of access to potentially curative therapies and treatment costs.

Pre-clinical and observational studies provide substantial evidence that aspirin may prevent or delay the development of cancer and metastases (4, 5). Many observational studies have demonstrated an association between aspirin use and a decreased risk of developing cancer (3, 6), particularly for gastro-oesophageal and colorectal cancer (Table 1). For example, the relative risk (RR) of developing oesophageal cancer in aspirin users compared to non-users is estimated to be 0·75, 95% confidence interval (CI) 0·62-0·89 (7-9). Similar effects are seen for several other common cancers including gastric, colorectal, pancreatic, ovarian, breast and prostate cancer. Most recently an epidemiological study of 63,605 patients who had received *Helicobacter pylori* eradication therapy reported a relative risk reduction of 70% in the development of gastric cancer with aspirin use (HR 0·30, 95% CI 0·15-0·61) (10).

Meta-analyses of randomised-controlled trials (RCTs) designed to investigate the cardiovascular effects of aspirin support the observations that aspirin reduces the risk of developing cancer. Long-term follow up of approximately 77,000 trial participants demonstrates a reduced risk of fatal cancer in those allocated to aspirin compared to placebo (11, 12). The greatest effects were seen in oesophageal and colorectal cancer, with a reduction in the 20-year risk of death from oesophageal cancer of 58% (hazard ratio (HR) 0·42, 95% CI 0·25-0·71, p=0·001) and for colorectal cancer death (HR 0·60, 95% CI 0·45-0·81, p=0·0007) (11, 13). Further analysis attributed the reduction in cancer mortality with aspirin to a reduction in the risk of metastases both at presentation (HR 0·69, 95% CI 0·38-0·77, p=0·0007) and subsequently (HR 0·45, 95% CI 0·28-0·72, p=0·0009).

Substantiating the hypothesis that aspirin reduces the risk of metastases several non-randomised cohort and population studies (also summarised in **Table 1**) demonstrate that aspirin use after a cancer diagnosis reduces both cancer mortality and overall mortality compared to non-use. For example, a recent Dutch population-based study of 13,000 patients with gastrointestinal cancer showed a marked reduction in overall mortality of 48% (HR 0·52, 95% CI 0·44-0·63) in aspirin users post diagnosis compared to non-users (14). Similarly, a study of more than 1700 patients in China who underwent surgical resection for gastro-oesophageal cancer reported a five-year survival of 51·2% in those patients allocated to daily aspirin post-operatively compared to only 41% on placebo (p=0·04) (15).

Based on these studies, several large, long-term randomised trials are underway to assess the benefit of aspirin after radical cancer therapy. The largest and most comprehensive is the Add-Aspirin protocol (ISRCTN74358648), which encompasses individually powered phase III trials in 4 common tumours gastro-oesophageal, colorectal, breast and prostate cancer. A pre-planned feasibility analysis (after two years of recruitment) was incorporated into the Add-Aspirin trial to assess recruitment, tolerability, and adherence, and to address any concerns about toxicity, particularly gastrointestinal bleeding, on aspirin after radical cancer therapy. We present this analysis for all tumour cohorts to provide reassurance about the use of aspirin after radical cancer therapy.

Method*:*

Study Design and Participants: The Add-Aspirin protocol has been described in detail previously. In brief, the main eligibility criteria, across the four tumour cohorts, include completion of a standard radical potentially curable treatment schedule (which may include surgery +/- neoadjuvant or adjuvant oncological management or primary chemoradiation (CRT)), with no evidence of residual disease or metastases. Patients already receiving aspirin, other anti-coagulants or long-term non-steroidal anti-inflammatory drugs are excluded. The gastro-oesophageal trial includes patients with histologically confirmed adenocarcinoma or squamous cell carcinomas of the oesophagus, gastro-oesophageal junction or stomach and the colorectal trial patients with adenocarcinomas stage II/III (and stage IV with

completely resected liver metastases only). Participants (in all cohorts) are over the age of 16, with no upper age limit, and have a performance status of 0-2. Exclusion criteria include evidence of moderate/severe renal impairment (glomerular filtration rate (eGFR) <45ml/min/1.73m^2), and liver function tests greater than 1.5x the upper limit of normal. Participants with a history of active or previous peptic ulceration or gastrointestinal bleeding within the last year, except where the cause of bleeding has been surgically removed, are excluded. All participants provide fully informed written consent.

Randomisation and masking: Randomisation is via a central system at the coordinating trials unit, accessible by phone to recruiting teams. Participants <75 years are randomised (1:1:1) to receive either aspirin 100mg, aspirin 300mg or a matched placebo to be taken daily for at least five years. Those aged 75 years or older are randomised 2:1 to aspirin 100mg or matched placebo only, due to increased risks of toxicity with higher doses and older age (16). For both age groups, allocation uses a minimisation algorithm based on key prognostic factors (specific to tumour type and not listed here to protect the integrity of the ongoing trial) and incorporating a random element. Use of matching placebos and identical drug packs ensures that participants and investigators remain blind to treatment allocation.

Procedures: Participants are initially registered onto the run-in phase of the study and receive aspirin 100mg oral daily open-label for eight weeks. In the gastro-oesophageal cohort this can commence between six and fourteen weeks after surgery, up to fourteen weeks after the final fraction of radiotherapy, or up to eight weeks after the end of adjuvant chemotherapy, depending on which treatment pathway has been undertaken; and in the colorectal cohort timelines are slightly shorter, commencing six to twelve weeks after surgery and up to six weeks after the final fraction of adjuvant radiotherapy or end of adjuvant chemotherapy. Participants in the breast cohort may receive endocrine therapy and trastuzumab concomitant with trial participation where appropriate, and similarly androgen deprivation therapy in the prostate cohort may be ongoing at the time of trial registration.

Dose reductions are not permitted in the run-in period; however time extensions are permitted if inadequate adherence is felt to be a temporary phenomenon. On completion of the run-in period,

adherence and tolerance of aspirin is assessed to determine suitability for subsequent randomisation. Participants experiencing any aspirin-related severe toxicity (grade ≥3 CTCAEv4), or significant (grade 3 or 4) gastrointestinal bleed, active gastrointestinal ulceration, new or worsening tinnitus (≥ grade 2), macular degeneration, intracranial bleeding or hypersensitivity to aspirin do not proceed to randomisation. Early versions of the protocol considered any grade of gastrointestinal bleeding, rather than grade 3 or 4 only, an aspirin related severe toxicity, with the newer version of the protocol commenced in December 2016 after 1,938 participants had already registered.

Outcomes: The primary outcome measure for the colorectal, breast and prostate cohorts is based on disease recurrence and is overall survival for the gastro-oesophageal cohort. Secondary outcome measures include adherence, toxicity, second malignancies and cardiovascular events. The overall recruitment target for entry into the run-in phase is 11,000 participants from centres across the UK, India and the Republic of Ireland, although at the time of the feasibility analysis only UK sites had commenced recruitment.

Statistical Analysis: The current analysis was based on recruitment rates, toxicity and adherence at the end of the run-in period, pre-planned two years after recruitment commenced. As a feasibility assessment, there was no comparative hypothesis nor associated power calculation. Analyses consisted of summary statistics (frequencies and percentages) based on data from the end of the run-in period including the proportion of participants proceeding to randomisation; tabulation of reasons for non-randomisation; participant reported adherence and aspirin-related toxicities (reported using CTCAE v4) by grade and according to protocol requirements for treatment discontinuation. All participants for whom the relevant data had been received at the time of analysis were included. Analyses were conducted using Stata (StataCorp LLC, v.15).

The Add-Aspirin trial (ISRCTN74358648, EudraCT 2013-004398-28) is being conducted in compliance with the Declaration of Helsinki 2008, the principles of Good Clinical Practice (GCP) and applicable national regulatory legislation. The protocol was approved by the South Central – Oxford C research ethics

committee and by local Research and Development departments at all participating UK centres; as well as by local ethics committees at all participating Indian sites. All participants provided written informed consent before registration. All authors had access to the study data and reviewed and approved the final manuscript. The Add-Aspirin study is registered as an International Standard Randomised Controlled Trial [ISRCTN74358648].

Role of the funding source:

The academic study sponsor, University College London (UCL), through the team at the MRC Clinical Trials Unit at UCL, along with the multi-disciplinary Trial Management Group, had full responsibility for the study design, the collection, analysis, interpretation of data, writing of the report, and in the decision to submit the paper for publication. The trial statisticians (FHC, SR, KK) had full access to all the data in the study and corresponding author had final responsibility for the decision to submit for publication, in discussion with the independent data monitoring and trial steering committees.

Results:

Trial Recruitment: Recruitment commenced in October 2015 and, by October 2017, 3494 participants were registered from 150 centres across the UK (sites across India and the Republic of Ireland had yet to open to recruitment at the time of the feasibility analysis). The target registration rates were gastro-oesophageal 2,350 in six years, colorectal 2,900 in three and a half years, breast 3,450 in three and a half years and prostate 2,350 in five years. Overall recruitment was good with registration rates exceeding the early estimated targets in the breast and prostate cohorts, but the gastro-oesophageal registrations in particular were slower than expected. At the time of the feasibility analysis, 115 were registered to the gastro-oesophageal cohort, 950 to the colorectal cohort, 1,675 to the breast cohort and 754 to the prostate cohort, with an average accrual rate of 167 registrations a month [Table 2]. Figure 1 shows the consort diagram for this analysis with end of run-in data available for 2253 participants at the time of the analysis.

Baseline Characteristics: Baseline characteristics of all participants from the breast, colorectal, gastro-oesophageal and prostate cohorts were as expected [Table 3]. Median age was lowest in the breast participants (52 years), and highest in the prostate participants receiving radical radiotherapy (71 years). In the gastro-oesophageal cohort, participants were predominantly male (81%) and histology adenocarcinoma in 82% (68/83), with only 18% (15/83) squamous cell carcinoma. Most participants in the colorectal and gastro-oesophageal cohort were stage III (61% and 52% respectively). Most participants in the breast, colorectal and gastro-oesophageal cohorts had received chemotherapy, either neo-adjuvant, adjuvant or both. All gastro-oesophageal patients who have received radical surgery were mandated to use a proton pump inhibitor (PPI) with trial treatment and at the time of registration 11% of the breast cohort, 18% colorectal, 13% prostate and 69% of gastro-oesophageal patients were already prescribed PPIs [Table 3].

Randomisation: The run-in period was still ongoing in 300/3494 participants at the time of the feasibility analysis. Of those who had completed the run-in phase 2719/3194 (85%) had proceeded to randomisation. This rate was similar across all the tumour-specific cohorts and close to the 90% rate anticipated in the trial design. End of run-in data was available for 2253 participants (end-of run-in case report forms are received within two to eight weeks of completing the run-in). The reasons for not proceeding to randomisation were often multifactorial, with minor toxicity (grade 1-2) and/or patient choice most frequent [Figure 1 and Table 4]. 69/83 (83%) of gastro-oesophageal participants registered were treated with primary surgery. 60/69 (87%) received neoadjuvant and/ or adjuvant chemotherapy, and 618/710 (87%) of the colorectal participants, with 30% of these still ongoing [Table 3]. Very few participants (1%, 26/2253 with end of run-in data available) experienced toxicity requiring protocol-mandated discontinuation of trial treatment. 2/26 were subsequently randomised after clinical review: one case of grade 3 hypertension, as the elevated blood pressure returned to normal on subsequent measurement; and one case of grade 2 tinnitus, which was deemed pre-existing and not felt to be related to trial treatment. Within the gastro-oesophageal cohort, only two participants (3%) experienced toxicity requiring discontinuation, one with grade 3 oesophageal pain and one grade 2 rectal bleed. The protocol

has subsequently been amended to allow participants with minor bleeding or bruising (grade 1-2) during the run-in period to continue in the trial, at the discretion of the investigator.

Adherence: Adherence was generally good with 95% (2148/2253) taking 6-7 tablets per week, similar across the four cohorts (70/75, 93% of the gastro-oesophageal cohort; 578/602, 96% of the colorectal cohort), assessed using patient self-reporting, review of used blister packs and diary cards.

Toxicity: 13/2253 (0·6%) reported grade 3 toxicities during the run-in period and no grade $\geq$3 gastrointestinal bleeds were reported [Table 5]. 26% (157/602) of colorectal participants were receiving ongoing chemotherapy at the time of toxicity, and 17% of gastro-oesophageal. With the exception of the one participant experiencing grade 3 oesophageal pain, no other grade $\geq$3 toxicity occurred in the gastro-oesophageal cohort. The most frequent grade 1 or 2 toxicity reported during the run-in period across all cohorts was dyspepsia (246/2253, 11%), with grade 1-2 bruising the second most frequent (211/2253, 9%). Only one (1/602, 0·2%) participant experienced a grade 1 upper gastrointestinal bleed in the colorectal cohort, with no instances of upper gastrointestinal bleed of any grade in the gastro-oesophageal cohort during the run-in period. 15/2253 (0.6%) of all participants experienced a grade 1-2 lower gastrointestinal bleed, only one of which were in the gastro-oesophageal cohort. There were no grade 4 toxicities or treatment related deaths in any cohort.

Discussion:

The Add-Aspirin study is designed to assess the effect of aspirin on the prevention of metastases and disease recurrence following radical cancer therapy in high risk individuals. The data presented show aspirin is well tolerated after radical therapy including surgery or chemoradiation, acceptable to patients, and there is no early evidence of increased toxicity in patients who received radical therapy for gastro-oesophageal cancer compared to the other common solid tumours within the Add-Aspirin protocol.

The study has also demonstrated marked differences in recruitment rates across the 4 common cancers. Some of this variance is not unexpected. Gastro-oesophageal cancer, for example, is less common in high

income countries and fewer patients complete a radical treatment pathway. Shared risk factors with cardiovascular disease, particularly smoking, mean more potential participants are already prescribed aspirin and therefore ineligible for the study. However, the recruitment rates have been in line with predictions for the breast and prostate cohorts but below the anticipated rates in the gastro-oesophageal and colorectal cohorts, although the rationale for evaluating aspirin as a therapy to prevent recurrence is strongest for these tumour types. Long-term data from randomised vascular trials demonstrate that the greatest effect of aspirin in reducing cancer mortality was seen for gastrointestinal adenocarcinomas (20 year risk of gastrointestinal cancer death HR 0·46, 95% CI 0·27-0·77, with benefits greatest for adenocarcinomas HR 0·66, 95% CI 0·56-0·77)(11).

Recently reported randomised trials further support the rationale that aspirin prevents tumour development particularly in the gastrointestinal tract. In the phase III AspECT trial (NCT00357682) in Barrett's metaplasia, the combination of a high dose proton pump inhibitor with 300mg of aspirin was demonstrated to significantly lengthen the time to event outcome, a composite of high grade dysplasia, oesophageal adenocarcinoma and all-cause mortality (17). Only 1% (28/2557) of participants experienced study-treatment-related grade 3-5 adverse events, of which only 0·6% (15/2557) were aspirin-related. Similarly, the SeAfOod trial (ISRCTN05926847) has shown a decrease in the mean number of colorectal adenomas per patient with allocation to aspirin (adjusted incidence rate ratio 0·78, 95% CI 0·68-0·90), particularly in right sided and serrated adenomas, and there was no increased risk of gastrointestinal adverse events in the aspirin group compared to placebo (18).

In 2016, the US Preventative Task Force recommended initiating low dose aspirin for the primary prevention of cardiovascular disease (CVD) and colorectal cancer in adults aged 50 to 59 years who have a 10% or greater ten-year CVD risk, are not at increased risk for bleeding, and have a life expectancy of at least ten years(19). Despite this, concerns about the use of aspirin for cancer chemoprevention and the risk of serious bleeding continue (20). Aspirin does increase the risk of bleeding though the magnitude of this effect is often over-estimated. The most extensive randomised data from the Antithrombotic Trialists'

Collaboration meta-analysis encompassing ~95,000 individuals demonstrated only a very modest increase in the risk of extracranial and major gastrointestinal bleeds from 0·07% per year to 0·1% per year on aspirin compared to control, with a similar small difference in the risk of intracranial bleeds (control 0·03% per year vs aspirin 0·04% per year, p=0·05) (21). No intracranial bleeds were reported during this feasibility analysis. The vast majority of bleeding episodes (excluding intracranial bleeding) related to aspirin resolve without sequelae (20), and in the vascular setting are generally considered to be outweighed by the benefits gained from aspirin, namely the prevention of secondary CVD events. From a population perspective, Cuzick *et al* have estimated that for every 100 men or women who start taking aspirin at the age of 55, over a 20 year period, the benefits on cancer mortality will be greater than on vascular mortality and outweigh the risks of serious bleeding (6).

Reluctance to prescribe aspirin for cancer prevention has been highlighted in a recent study of UK general practitioners. Aspirin reduces the incidence of cancer in people with Lynch Syndrome and is recommended in several clinical guidelines, including The National Institute for Health and Care Excellence (NICE) (22). Despite this, a study of 1,007 UK general practitioners revealed that almost 20% were unwilling to prescribe 300mg of aspirin daily despite a randomised trial demonstrating its cancer preventative effects in Lynch Syndrome (23). More than 30% of respondents were uncomfortable discussing the benefits and harms of aspirin with their patients, even with the recommendation from a secondary care clinician (23). This reluctance might partly explain the lower recruitment rates seen in the gastrointestinal cohorts of the Add-Aspirin study, particularly from physicians who treat patients with gastrointestinal bleeding. Several strategies are incorporated into the trial design to mitigate the bleeding risk on aspirin, including exclusion of individuals with a known increased risk of bleeding; randomising participants over the age of 75 years to only 100mg of aspirin or placebo (and not the higher aspirin dose), due to the increased risk of bleeding with both dose and age (16, 20); and use of a proton pump inhibitor for patients who have undergone gastrectomy or oesophagectomy, and recommended in those aged over 75 years (16). The data presented in this paper should provide further reassurance that the risk to participants is low.

Completing recruitment within the predicted timelines remains a challenge for many clinical trials. Recruitment predictions from potential sites are used to advise trial recruitment projections, and sites have been shown to over-estimate their predicted recruitment rates based on their maximum or best possible, rather than mean monthly recruitment (24). When trials are slow to recruit, the relevance of the clinical question or the acceptability of the randomisation is frequently cited as the reason. The Add-Aspirin protocol challenges these assumptions as the clinical question is the same across the tumour cohorts and there is no evidence that the randomisation is not acceptable to patients.

Recent results published from the ASPREE (ASPirin in Reducing Events in the Elderly) trial (NCT01038583), which recruited more than 19,000 healthy participants mainly, >70 years old, who were randomly allocated to aspirin 100mg daily or placebo, showed no difference in the primary outcome measure (a composite of death, dementia and permanent physical disability)(25). Subgroup analyses reported an increase in cancer mortality, subsequently attributed to an increase in the risk of incident metastatic cancer but with no increase in incident cancers overall (26). Possible explanations for this observation include an increase in bleeding from occult metastatic disease in this older cohort unmasking some cancers at an earlier stage. The severity and consequences of bleeding with aspirin is known to increase with age (16, 20). Follow up of the ASPREE trial is currently relatively short at 4.7 years, and longer term follow-up may provide more clarification (25). Given the substantial body of previous data on the cancer chemopreventative effects of aspirin, the subgroup analysis from the ASPREE trial has not undermined the rationale for the Add-Aspirin trial or the other ongoing adjuvant aspirin studies internationally. Opportunities for combining data from these trials will exist in the future.

To our knowledge, this is the most up-to-date and comprehensive data on the feasibility, toxicity and tolerability of aspirin use in breast, colorectal, prostate and gastro-oesophageal cancers after potentially curative therapy. One limitation to this study is that it is only relatively early data, but recent evidence suggests that the risk of bleeding events on aspirin reduces with time, most frequently occurring in the first few months of commencing treatment (16). As such, although only early data, it is likely to be a good

surrogate for the risk of future toxicity. More generally, since participants have all recently undergone major treatment, a significant amount of the reported toxicity in this study may be due to previous or ongoing other therapies. We also recognise that the measurements of adherence used are subject to recall bias, however translational sub-studies currently underway will also objectively measure adherence in this cohort of patients. Despite the challenging nature of radical therapy, particularly in the gastro-oesophageal cohort where post-operative complication rates have been shown to be as high as 30% and have a major detrimental impact on quality of life (27), this has not been reflected in the measured adherence to trial treatment and, as a result, rates of progression from run-in to randomisation have been close to the expected 90% in line with the other cohorts.

Conclusion

The rationale and supporting evidence for evaluating aspirin as a potential anti-cancer therapy is strong and completion of clinical trials specifically designed to assess this hypothesis is the next required step. Re-purposed medicines such as aspirin offer the potential for low cost therapies to improve cancer outcomes. Evidence-based information about potential efficacy and toxicity is required to help physicians conduct meaningful discussions with potential participants about trial participation.

Supplementary Attachment:

Add-Aspirin protocol

Appendix – Table 1 and Table 4

Author Contributions:

RL is chief investigator. **NJ** and **RL** drafted the manuscript. **RL** conceived the study concept and design. **NJ, RH, DS, SS, KG, SF, KP, NW, VK, JG, TI, JB, AC, VH, DG, HK, AR, DC, TI, RA, AT, RW, CSP, RL** collected data. **SR, FC and KK** had access to the study data and contributed to the analysis and interpretation of the data. **All other authors** reviewed and approved the final manuscript.

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We would like to thank the study participants and their families, site research staff, and members of the wider Add-Aspirin trial management groups, trial steering committee and independent data monitoring committee.

We would like to acknowledge in particular Professor Carlo Patrono, Professor Peter Rothwell and Professor Sir John Burn who have provided specialist knowledge and expertise in the field of aspirin.

Declaration of Interest

The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care

RL and the MRC Clinical Trials Unit at UCL report non-financial support from Bayer Pharma AG (supply of trial drugs) during the conduct of the study. RL reports grants from CRUK and NIHR, and honorarium from the Aspirin Foundation during the conduct of the study. JB reports personal fees from Astrazeneca, personal fees from Roche, personal fees from Merck Serono, personal fees from BMS, grants and other from Incyte, other from MSD, personal fees and other from Amgen, outside the submitted work; RW reports other from Almac Discovery, personal fees from Servier, personal fees from Amgen, personal fees from Clovis Oncology, personal fees from Halozyme, personal fees from BMS, personal fees from Karus Therapeutics, personal fees from Roche, personal fees from AstraZeneca, personal fees from Pierre Fabre, personal fees from CV6 Therapeutics, outside the submitted work; All other authors declare no competing interests.

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FHC, SR, KK had full access to all the data in the study; RL had final responsibility for the decision to submit for publication in discussion with the (independent) trial oversight committees.

Data Sharing Statement: The Add-Aspirin trial data are held at MRC CTU at UCL, which encourages optimal use of data by employing a controlled access approach to data sharing (http://www.ctu.mrc.ac.uk/our_research/datasharing/). Requests for data can be made at any time and can be initiated by contacting mrcctu.ctuenquiries@ucl.ac.uk or through the URL: http://www.ctu.mrc.ac.uk/our_research/datasharing/application_process/. There is a formal application process, whereby the request will undergo review by the trial team, as well as independent researchers, to ensure that the proposed research is both ethical and has a strong scientific rationale. Data will not be released if it would compromise the ongoing trial. The specific data and associated documents to be shared will be dependent on the nature of the individual request and this will be documented in a formal data sharing agreement.

References:

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