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 (EudraCT# 2013-004398-28)

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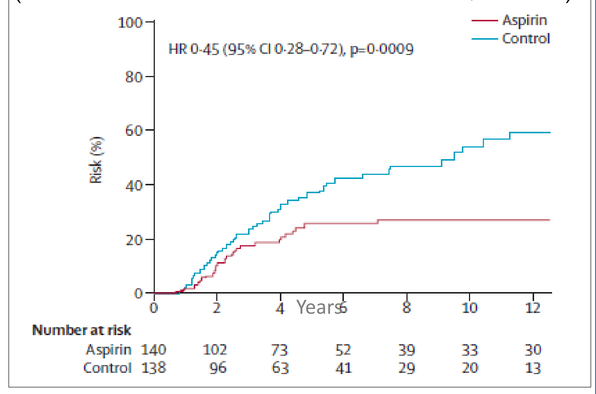
Scientific Background

Aspirin has the potential to be an effective adjuvant cancer therapy (1). This hypothesis has been strengthened by recent studies, described below and well-designed trials are needed.

Meta-analyses of cardiovascular trials

Meta-analyses of randomised-controlled trials (RCTs) designed to assess vascular effects of aspirin have shown reductions in cancer incidence and cancer mortality with regular aspirin use (2-5). Early reductions in mortality have been attributed to a decrease in the risk of metastases associated with aspirin (5) (see figure).

Effects of aspirin on risk of metastases after diagnosis of adenocarcinoma
(278 individuals with incident cancer in 5 RCTs, n>17000)



Randomised data

CAPP2 - the first RCT designed to show aspirin has beneficial effects on cancer outcomes with a positive result: aspirin 600mg daily prevented colorectal and other cancers associated with Lynch Syndrome) - hazard ratio (HR) 0.45 (95% CI 0.26-0.79, p=0.0005) for treatment ≥2 yrs (6).
Women's Health Study – with long-term follow-up aspirin reduced colorectal cancer incidence (HR, 0.80 [CI, 0.67 to 0.97]; P =0.021) (7).

Results from observational studies of regular aspirin use after a cancer diagnosis

Study	Cancer	Outcome	Risk reduction with aspirin use (HR or RR + 95% CI)
Nurses' Health and Health Professionals' Follow-up Studies (n=1279) (8)	Colorectal	Colorectal cancer mortality All cause mortality	HR = 0.71 (0.53, 0.95) HR = 0.79 (0.65, 0.97)
Dutch population-based study (n=4481) (9)	Colorectal	Overall survival	RR = 0.77 (0.63, 0.95)
Tayside/Fife population-based study (n=2990) (10)	Colorectal	Colorectal cancer mortality Overall mortality	HR = 0.58 (0.45, 0.75) HR = 0.67 (0.57, 0.79)
Nurses' Health Study (n=4164) (11)	Breast	Breast cancer mortality	RR = 0.36 (0.24, 0.54) daily use RR = 0.54 (0.41, 0.70) daily use
CaPSURE (n=5995) (12)	Prostate (post-radical therapy)	Prostate cancer mortality	HR = 0.43 (0.21, 0.87)
Liu *et al.* 2009 (n=1600) (13)	Gastro-oesophageal	Overall survival	5-year OS aspirin 51.2%, placebo 41%, no tablet 42.3% (no HR/RR presented)

Mechanisms of action

Pre-clinical data suggest a number of potential mechanisms of action. Low-dose daily aspirin has a 30 minute half life, and only negligible effects on targets other than platelets which are thought to play a role in the development and spread of cancer. Unlike other NSAIDs, aspirin binds irreversibly to Cyclooxygenase (Cox) resulting in decreased platelet aggregation. A decrease in platelet Cox-1 activity may lead to down-regulation of Cox-2 in tumours (14), and could explain why aspirin and selective Cox-2 inhibitors have anti-cancer effects.

Trial Rationale and Aims

Rationale

Add-Aspirin trial participants will have had potentially curative treatment for non-metastatic colorectal, breast, gastro-oesophageal or prostate cancer. These disease sites are those for which (i) evidence relating to a potential benefit of aspirin is strongest; (ii) potential impact is large (common cancers often diagnosed early, or with poor outcomes); and (iii) recruitment is considered feasible.

Aims

- To assess whether regular aspirin use after standard curative therapy can prevent recurrence and prolong survival in participants with non-metastatic common solid tumours
- To demonstrate that implementation of the intervention is feasible in a range of settings
- To assess the potential overall health benefits of aspirin in a population with non-metastatic cancer

Aspirin toxicity

Concerns about toxicity, particularly serious haemorrhage, may have limited use of aspirin in primary cancer prevention (15). Reported rates of serious bleeding on aspirin have been inconsistent (16).

The Anti-Thrombotic Trialists' Collaboration meta-analysis of 6 primary cardiovascular prevention RCTs (n>95,000, mean age 56, 46% male) estimated that aspirin increased the incidence of major extracranial bleeds from 0.07% to 0.1% per year and haemorrhagic strokes from 0.03% to 0.04% (17).

Measures to reduce the risks associated with aspirin in the trial include: eligibility criteria excluding those at high risk of bleeding, limiting those ≥75 years old to 100mg aspirin or placebo, use of a 8 week active run-in period and detailed guidelines for toxicity management.

Trial Design

A phase III, multi-centre, double-blind, placebo-controlled randomised trial with 4 parallel cohorts. In total, 9,920 participants recruited in the UK and India over 3 – 6 years.

Intervention

Active run-in period aspirin 100mg daily for approximately 8 weeks to identify those unlikely to tolerate therapy or have problems adhering.

Randomised to aspirin 100mg, aspirin 300mg or placebo daily for at least 5 yrs. Over 75 years old randomised between 100mg aspirin or placebo only. Follow-up within the trial for at least 5 years. In the UK, long-term data will also be obtained from routinely-collected healthcare databases.

Outcome measures

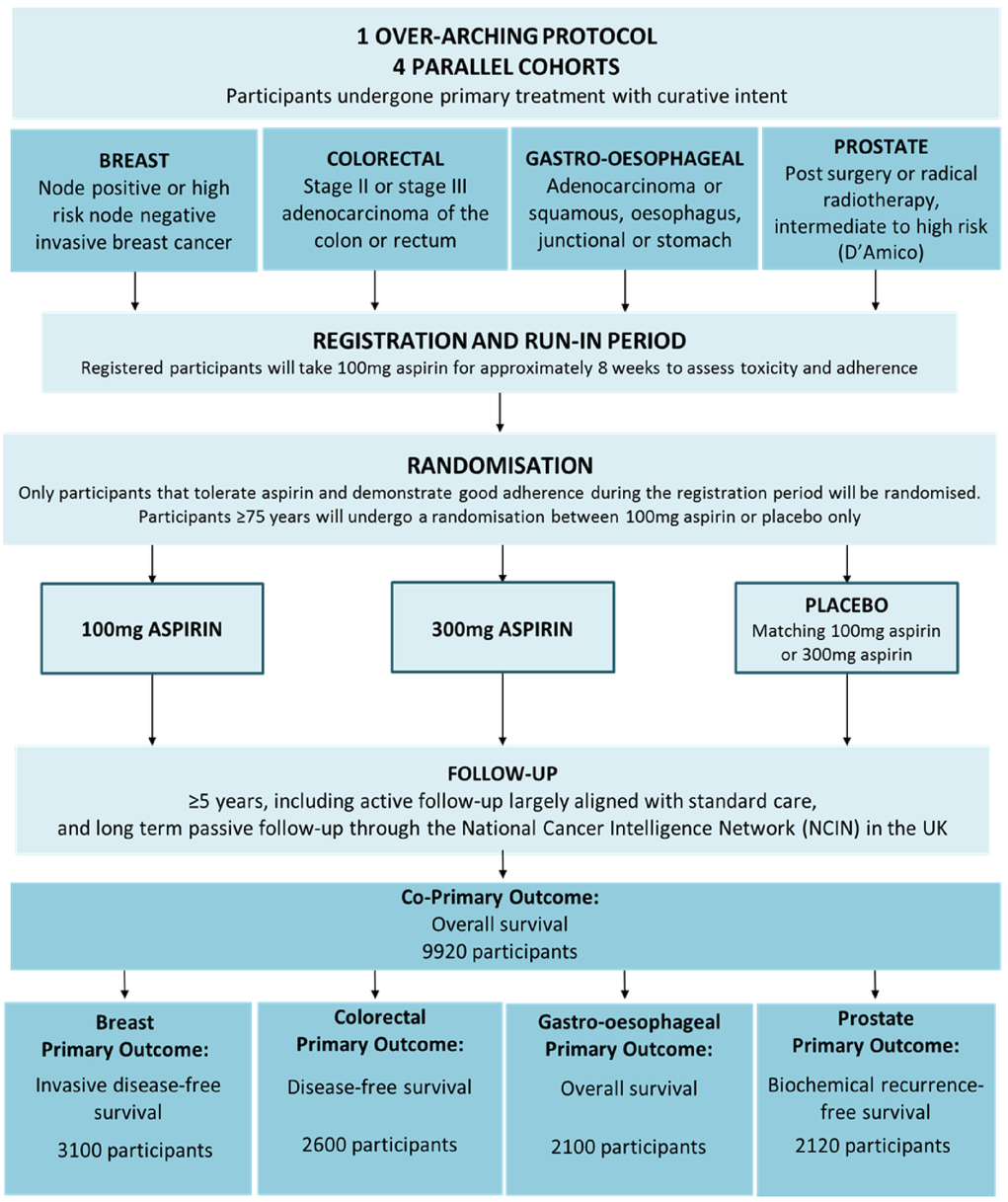
Primary outcome measures are tumour site-specific and the 4 cohorts are individually powered (see schema). A co-primary outcome measure to assess overall survival across all cohorts. Secondary outcome measures include adherence, toxicity and cardiovascular events.

Feasibility stage

The trial incorporates a feasibility phase (~$2^1/_2$ years) during which recruitment feasibility, treatment adherence and safety will be assessed.

Translational research

Subject to funding, a large bio-bank and programme of associated correlative science is planned.



Organisation

- Sponsored by the **University College London** (UCL) and coordinated by the **MRC Clinical Trials Unit at UCL** in London.
- **Cancer Research UK** are funding the trial (C471/A15015). Contract negotiations are being finalised with a further funding agency.
- International trial with centres in the UK and India (breast and gastro-oesophageal only) with Indian participation co-ordinated by the **Tata Memorial Hospital, Mumbai**.
- Trial email: **Add-Aspirin@ctu.mrc.ac.uk**.

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