The Add-Aspirin Trial: Aspirin as Adjuvant Treatment for Colorectal Cancer

Ruth E Langley[1], Richard H Wilson[2], Fay H Cafferty[1], Nalinie Joharatnam[1], Janet Graham[3], Daniel Swinson[4], Tim Iveson[5], Farhat Din[6], Robert Steele[7], Verity Henson[8], Anne Crossley[9], CS Pramesh[10], Gregory Leonard[11], Axel Walther[8], Richard Adams[12], Lesley Dawson[13], Roshan Agarwal[14], Komel Khabra[1], Mahesh Parmar[1]

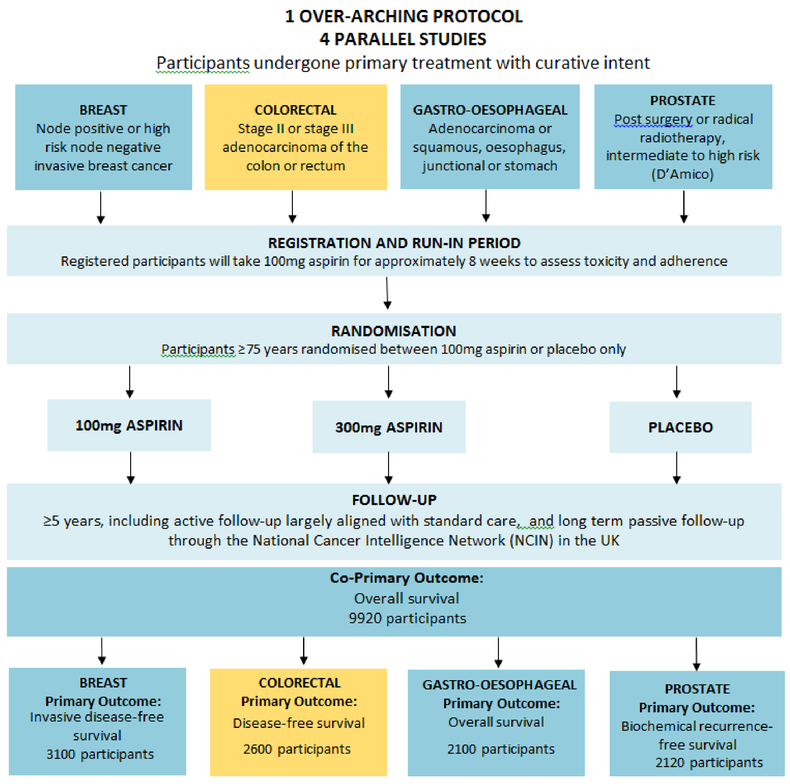
Background

Add-Aspirin is an international, phase III trial aiming to assess whether regular aspirin use can prevent recurrence and improve survival following surgery (+/- relevant adjuvant therapy) for colorectal adenocarcinoma. Parallel trials are investigating the question in early stage breast, prostate and gastro-oesophageal cancer following potentially curative treatment.

There is now a significant body of evidence indicating a potential role for aspirin in colorectal cancer (CRC) prevention, as well as in a number of other tumour types. Much of the evidence comes from meta-analyses of cardiovascular trial data, where effects on incidence of cancer metastases and short-term mortality suggest a further possible role in the treatment setting. This is supported by observational studies of aspirin use after cancer diagnosis.

In the prevention setting, aspirin use has been limited by toxicity concerns, particularly of serious bleeding. In the adjuvant setting, benefits associated with reducing recurrence and subsequent treatment may outweigh these risks. The Add-Aspirin trial will investigate this, and will also consider possible mechanisms of action for aspirin effects, including the impact of PIK3CA mutations, where there are currently several theories and conflicting data.

As a low cost, generic and widely available drug, which is generally safe, if aspirin is shown to be effective, it could have a huge impact on cancer outcomes globally. International recruitment is a key aspect of the Add-Aspirin trial, allowing the intervention to be assessed in a wide range of settings and greatly increasing the potential impact of results.



Method

Design: The Add-Aspirin CRC trial is an international, phase III, double-blind, randomised, placebo-controlled trial incorporating an active run-in period. It forms part of a basket trial with three other separately powered, tumour-specific cohorts (see figure).

Participants: Individuals who have undergone surgery and relevant adjuvant treatment for stage II or III CRC, as well as those with completely resected CRC liver metastases.

Interventions: All participants are asked to take aspirin 100mg daily for an 8-week run-in period to identify those likely to tolerate and adhere to the trial intervention. Those suitable to proceed are randomised (1:1:1) to aspirin 100mg, aspirin 300mg or placebo daily for at least 5 yrs.

Outcomes: The primary outcome for the CRC cohort is disease-free survival (DFS). Overall survival will be assessed as a co-primary outcome measure across all cohorts. Secondary outcome measures include adherence, toxicity and cardiovascular events.

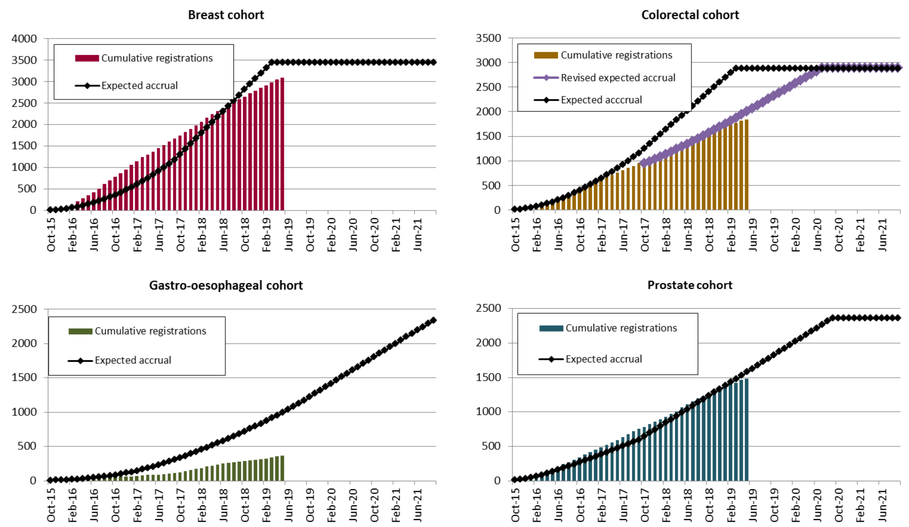
Managing toxicity: Eligibility criteria and the run-in period ensure that individuals with an increased risk of serious toxicity are not included. Participants ≥75 years are randomised between 100mg aspirin or placebo only (due to increased risks of bleeding associated with older age and higher doses), and investigators are advised to consider co-prescription of a proton pump inhibitor for these individuals. Blood pressure checks and other measures ensure symptoms are monitored and managed appropriately.

Sample size: The trial is designed to have 90% power to detect a 5% improvement in DFS at 5 years with a HR of 0.80. n=2600 randomised participants are needed. A pre-specified, powered subgroup analysis will consider the impact of PIK3CA mutation status

Feasibility: A pre-planned feasibility phase considered data on recruitment in the first 2 years, as well as adherence and toxicity reported during the run-in period.

Recruitment and feasibility data

The trial opened in October 2015 and recruitment is progressing well (see figure). To date, **1839** patients have been registered in the CRC cohort (**1491** randomised). Across the 4 cohorts, a total of **6782** participants have been registered (**5521** randomised). The trial is now open in 196 centres across UK, India and the Republic of Ireland. CRC recruitment is expected to be complete towards the end of 2020 (5 years, revised from 3 ½ years originally).



Feasibility assessment: 3494 participants (950 CRC) were registered in the first 2 years. Run-in data on 2253 patients (including 602 with CRC) who received 100 mg PO aspirin in an open-label fashion for 8 weeks was assessed to check on the tolerability, adherence, and the subsequent rate of randomisation to 0, 100 and 300 mg PO aspirin daily.

Contact us

The trial Chief Investigator is **Professor Ruth Langley (MRC CTU at UCL)** and the CRC leads in the UK, Republic of Ireland and India are **Richard Wilson (Glasgow)**, **Greg Leonard (Cancer Trials Ireland)** and **Dr Avanish Saklani (Tata Memorial Centre)** respectively**.** For further information, visit the Add-Aspirin website or contact us:

Gemma Sancha, Tessa Dibble, Alex Robbins (Trial Managers)
Tel: 020 7670 4892/4759/4906
Email: mrcctu.add-aspirin.ucl.ac.uk
Website: www.addaspirintrial.org

1. MRC Clinical Trials Unit at UCL; 2. University of Glasgow; 3. Beatson West of Scotland Cancer Centre; 4. St James's University Hospital, Leeds; 5. University Hospital Southampton; 6. University of Edinburgh; 7. University of Dundee; 8. University Hospitals Bristol; 9. Leeds Teaching Hospitals; 10. Tata Memorial Centre, Mumbai; 11. Cancer Trials Ireland; 12. Cardiff University and Velindre Cancer Centre; 13. Edinburgh Cancer Centre; 14. Northampton General Hospital.

Add-Aspirin is jointly funded by Cancer Research UK (C471/A15015, www.cancerresearchuk.org), the National Institute for Health Research Health Technology Assessment Programme (12/01/38, www.nihr.ac.uk) and the MRC Clinical Trials Unit at UCL.