Aspirin use after radical cancer therapy – feasibility and toxicity data from the Add-Aspirin trial

N. Joharatnam[1], F. Cafferty[1], S. Rowley[1], M. Scott-Brown[2], C. Price[3], D. Swinson[4], R. Hubner[5], A. Ring[6], R. Wilson[7], H. Kynaston[8], D. Gilbert[1], D. Cameron[9], F. Din[9], A. Thomas[10], J. Jankowski[11], A. Walther[12], D. Eaton[13], N. Ainsworth[14], R. Kerr[15], L. Hughes-Davies[16], M. Parmar[1], C.S Pramesh[17], S. Gupta[17], R. Langley[1], on behalf of the Add-Aspirin Trial Management Group.

[1]Medical Research Council Clinical Trials Unit, London, UK; [2] University Hospitals Coventry & Warwickshire, Coventry UK; [3] Worcestershire Royal Hospital, Worcester, UK; [4] St James' University Hospital, Leeds, UK; [5] The Christie Hospital, Manchester, UK; [6]The Royal Marsden Hospital, London, UK; [7] Belfast City Hospital, Northern Ireland, UK; [8]University Hospital of Wales, Cardiff, UK; [9] Western General Hospital, Edinburgh, UK; [10] Royal Leicester Infirmary, Leicester, UK; [11]Office of Research and Innovation & Royal College of Surgeons, Ireland; [12] Bristol Haematology & Oncology Centre, Bristol, UK; [13] Royal Lancaster Infirmary, Lancaster, UK;.[14] Queen Elizabeth Hospital, King's Lynn, UK; [15] Churchill Hospital, Oxford, UK; [16]Addenbrookes Hospital, Cambridge, UK;[17]Tata Memorial Hospital, Mumbai, India.

Background

Pre-clinical, observational and randomised evidence suggests aspirin may prevent or delay the development of cancer and metastases, and is strongest for colorectal and gastro-oesophageal cancer. However, concerns around feasibility, adherence and tolerability (particularly serious bleeding) have limited aspirin use for cancer chemoprevention.

A major part of the evidence base relating to aspirin & cancer has emerged from randomised controlled trials designed to evaluate the vascular effect of aspirin. Meta-analyses of individual patient data from 51 randomised trials with ~77,000 participants have demonstrated a decreased cancer incidence (hazard ratio HR 0.81 (95% CI 0.7-0.93)) with treatment for >5yrs and reduced cancer deaths by approximately 15%, particularly adenocarcinomas of the gastrointestinal tract (1).

The evidence for an effect of aspirin in the treatment setting is particularly strong for gastro-oesophageal cancer. The recently published AspECT trial has added to this, suggesting a potential role for the combination of aspirin and esomeprazole in Barretts oesophagus (time ratio TR 1.59, 95% CI 1.14–2.23, p=0·0068: time to event composite of high grade dysplasia, oesophageal cancer or death) with very low rates of toxicity (1% reported study-treatment-related serious adverse events) (2).

Method

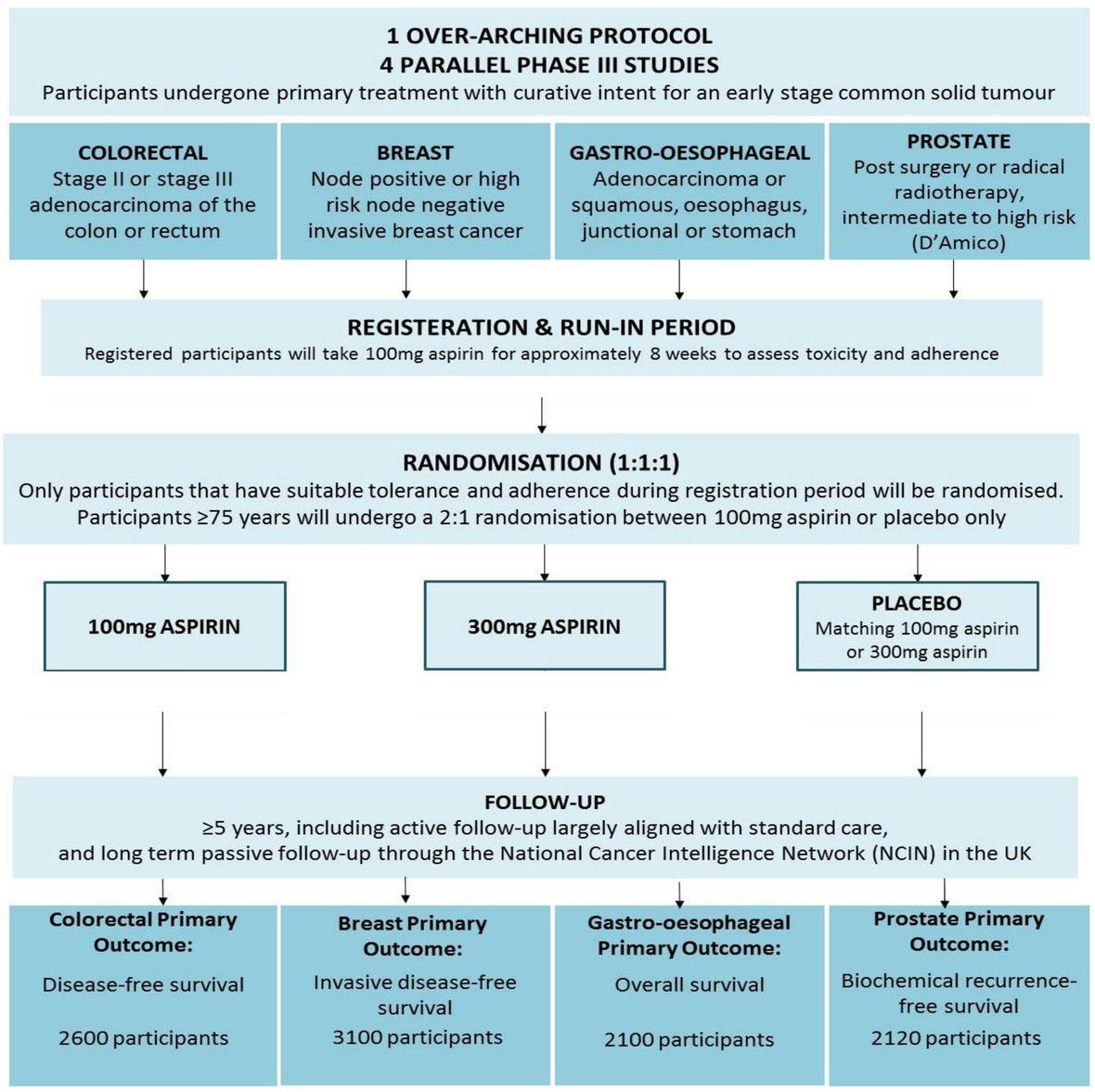
Add-Aspirin is a double-blind, randomised-controlled trial encompassing 4 individually powered phase III trials in early-stage breast, prostate, colorectal and gastro-oesophageal cancer, evaluating the effect of aspirin after radical therapy (3).

All participants initially take open-label aspirin (100mg daily) for 8 weeks (run-in), to assess adherence and toxicity prior to randomisation (1:1:1, aspirin 300mg, aspirin 100mg or matched placebo for ≥5 years).

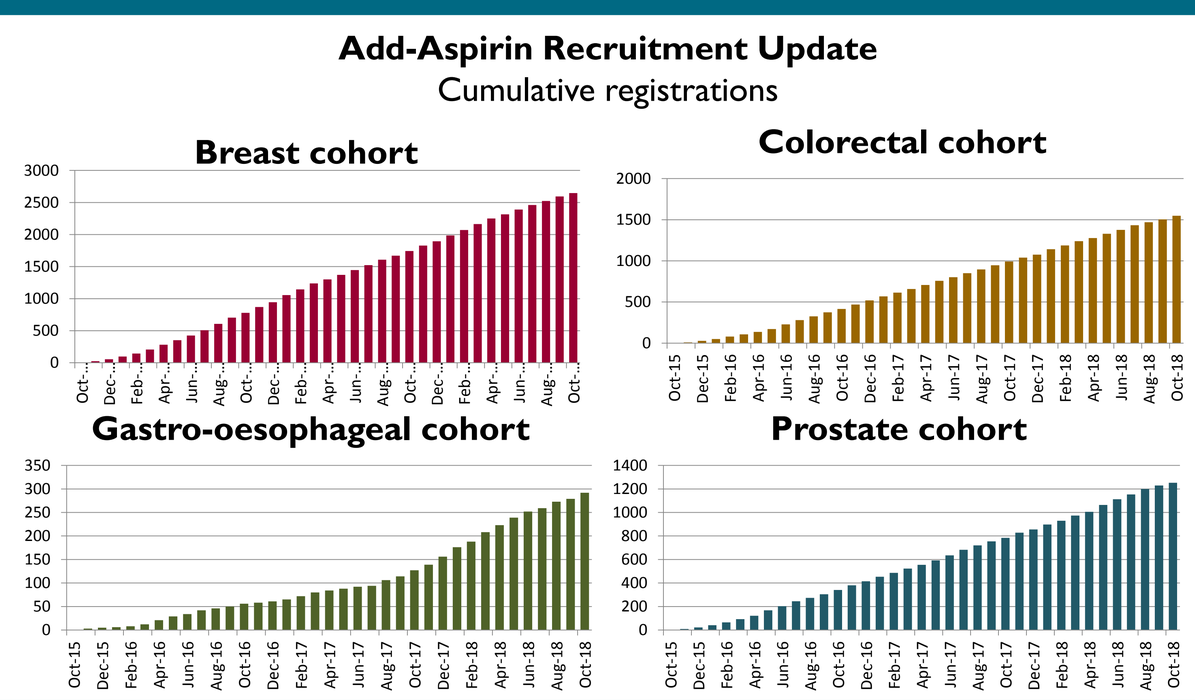
Measures to reduce the risks associated with aspirin have been implemented (e.g. exclusion of patients with a recent ulcer or bleed; blood pressure monitoring; avoiding concomitant NSAIDs; randomisation to only 100mg and placebo for those >75 years; PPI prophylaxis post oesophagectomy and gastrectomy).

A pre-planned feasibility analysis was performed to assess tolerability and adherence when >2000 participants had completed the run-in period.

Trial Design



Recruitment



Results

Between October 2015 and October 2017, 3494 of a targeted 11000 participants were registered from 165 sites in the UK; recruitment rates differed across tumour sites compared to predictions.

Run-in data (n=2253) showed good adherence: 95% took 6-7 tablets/week and 85% proceeded to randomisation, with rates consistent across tumour cohorts. Main reasons for not proceeding to randomisation were toxicity (mostly minor grade 1/2) and/or patient choice, with only 0.7% (16/2253) of participants experiencing toxicity requiring discontinuation during the run-in.

Toxicities Reported During the Run-In Period

		Breast	Colorectal	OG	Prostate
		n=1113	n=602	n=75	n=463
Dyspepsia	Grade 1-2	138 (12%)	51 (8%)	10 (13%)	47 (10%)
	Grade 3-4	0 (0%)	2 (0%)	0 (0%)	0 (0%)
Bruising	Grade 1-2	133 (12%)	53 (9%)	2 (3%)	23 (5%)
	Grade 3-4	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Lower GI bleed	Grade 1-2	4 (0%)	6 (1%)	1 (1%)	3 (1%)
	Grade 3-4	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Upper GI bleed	Grade 1-2	0 (0%)	1 (0%)	0 (0%)	0 (0%)
	Grade 3-4	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Fewer than 1% (13/2253) experienced a grade ≥ 3 toxicity, similar across tumour groups (including one lower gastrointestinal bleed in a prostate cancer participant; no upper gastrointestinal bleeds).

Conclusion

The data demonstrate that aspirin is well-tolerated over an 8-week run-in, and acceptable to patients after radical cancer therapy, with low toxicity rates in all tumour cohorts, including gastro-oesophageal participants.

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. Trial recruitment continues with >5700 participants now registered from the UK, India and Republic of Ireland.

Disclosures

The trial is being jointly funded by Cancer Research UK (grant number C471 /A15015), The National Institute for Health Research Health Technology Assessment Programme (project number 12/01/38), The MRC Clinical Trials Unit at UCL. In India, the Sir Dorabji Tata Trust provides funding. In the Republic of Ireland, Cancer Trials Ireland provide additional support. Bayer Pharmaceuticals AG is providing aspirin and placebos.

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

Trial email: mrcctu.add-aspirin@ucl.ac.uk

REFERENCES 1. Rothwell *et al.* Lancet, 2010, 2011, 2012. 2. Jankowski *et* al, Lancet. 2018;392:400-408. 3. Coyle C, *et al.,* Contemporary Clinical Trials. 2016;51:56-64.