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Overview

Co-enrolment of Participants into Multiple Cancer Trials: Benefits and Challenges

F.H. Cafferty *, C. Coyle *, S. Rowley *, L. Berkman †, M. MacKensie ‡, R.E. Langley *

* MRC Clinical Trials Unit at UCL, London, UK
† NCRI Consumer Liaison Group, London, UK
‡ Independent Cancer Patient Voices, London, UK

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Abstract

Opportunities to enter patients into more than one clinical trial are not routinely considered in cancer research and experiences with co-enrolment are rarely reported. Potential benefits of allowing appropriate co-enrolment have been identified in other settings but there is a lack of evidence base or guidance to inform these decisions in oncology. Here, we discuss the benefits and challenges associated with co-enrolment based on experiences in the Add-Aspirin trial – a large, multicentre trial recruiting across a number of tumour types, where opportunities to co-enrol patients have been proactively explored and managed. The potential benefits of co-enrolment include: improving recruitment feasibility; increased opportunities for patients to participate in trials; and collection of robust data on combinations of interventions, which will ensure the ongoing relevance of individual trials and provide more cohesive evidence to guide the management of future patients. There are a number of perceived barriers to co-enrolment in terms of scientific, safety and ethical issues, which warrant consideration on a trial-by-trial basis. In many cases, any potential effect on the results of the trials will be negligible – limited by a number of factors, including the overlap in trial cohorts. Participant representatives stress the importance of autonomy to decide about trial enrolment, providing a compelling argument for offering co-enrolment where there are multiple trials that are relevant to a patient and no concerns regarding safety or the integrity of the trials. A number of measures are proposed for managing and monitoring co-enrolment. Ensuring acceptability to (potential) participants is paramount. Opportunities to enter patients into more than one cancer trial should be considered more routinely. Where planned and managed appropriately, co-enrolment can offer a number of benefits in terms of both scientific value and efficiency of study conduct, and will increase the opportunities for patients to participate in, and benefit from, clinical research.

Key words: Adjuvant; aspirin; cancer; co-enrolment; randomised controlled trial

Statement of Search Strategies Used and Sources of Information

The paper largely reflects expert opinions and experiences of the authors, and their knowledge of the literature. The Pubmed database was searched for relevant articles, but a formal search strategy was not defined.

Introduction

Co-enrolment – entering patients into more than one clinical trial either concurrently or sequentially – is rarely reported or discussed in oncology literature. As such, co-enrolment policies may be specified in the trial protocol or decisions made by an institute or recruiting investigator, without a clear rationale or evidence base. With a lack of guidance or consensus on when co-enrolment is appropriate, it is unsurprising that the decision not to co-enrol may be seen as the safe option.

Recent trends in oncology research – such as the use of longer term, maintenance therapies and evaluation of repurposed agents (whose use alongside other treatments may already be well documented) – as well as the ever-increasing number of trials competing for the same patients, mean that co-enrolment is becoming more relevant. More routine consideration of opportunities to enter patients into multiple trials is warranted.

Author for correspondence: F.H. Cafferty, MRC Clinical Trials Unit at UCL, Aviation House, 125 Kingsway, London WC2B 6NH, UK. Tel: +44-20-7670-4868.
E-mail address: f.cafferty@ucl.ac.uk (F.H. Cafferty).

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Co-enrolment has been explored in other (non-cancer) settings – particularly those where trial recruitment is challenging and/or there are many (large) competing trials – including resuscitation [1], critical care [2–4] (including neonatal [5] and paediatric [6] settings) and peri-natal research [7]. Here, co-enrolment offers the opportunity to maximise use of the patient population and increase the speed and efficiency of research delivery. In settings such as HIV [8] and anaesthesia [9], where large, pragmatic trials are common and/or participants might be receiving several other medications, co-enrolment may also provide important data on drug interactions.

Across different settings, researchers report barriers to co-enrolment and, frequently, a lack of (universal) support from the research community or ethics committees [2,6,9]. Common barriers range from ethical and scientific considerations to safety concerns [1–3,6,7,9]. The need for further reporting of co-enrolment and more research on this topic, is noted [4,7,10].

The potential benefits of co-enrolment, as well as possible barriers, are relevant in oncology trials and warrant further exploration. Here, we report our experiences with exploring and managing co-enrolment opportunities within a large, multicentre oncology trial.

The Add-Aspirin Trial

The Add-Aspirin trial is a randomised controlled trial (RCT) assessing whether regular aspirin use after curative treatment for an early stage tumour can prevent recurrence and prolong survival (Figure 1) [11–13]. The intervention is being tested in four tumour types (breast, colorectal, gastro-oesophageal and prostate) by means of parallel cohorts. Patients enrol following potentially curative therapy – this incorporates a range of treatment pathways for each tumour site, including surgery with any appropriate (neo-) adjuvant therapies, radical chemoradiation (oesophageal) and radical radiotherapy (prostate). Participants are randomised to daily aspirin 100 mg, 300 mg or placebo. The trial is recruiting across the UK, and will also open in India, with a target of approximately 10 000 participants.

Co-enrolment may be relevant to patients entering Add-Aspirin subsequent to enrolling in a primary therapy trial and may also arise at the time of recurrence during participation in Add-Aspirin. A proactive approach to exploring co-enrolment opportunities with other trial teams has been adopted to agree when this might be appropriate and how it can be facilitated and managed within the ongoing trials.

Benefits of Co-enrolment

Co-enrolment is particularly relevant in Add-Aspirin as the intervention is being given after initial treatment, so participants from trials of primary therapies represent a significant proportion of the eligible population. However, the potential advantages of co-enrolment apply more widely to multicentre oncology RCTs – particularly pragmatic trials – as a number of different interventions will be relevant to a patient over the course of their disease and treatment. Allowing appropriate co-enrolment improves the efficiency of recruitment, helping to ensure the feasibility of trials running concurrently, and maximises opportunities for patients to participate in, and benefit from, clinical research.

A further advantage is the opportunity to assess trial interventions alongside one another, helping to ensure the

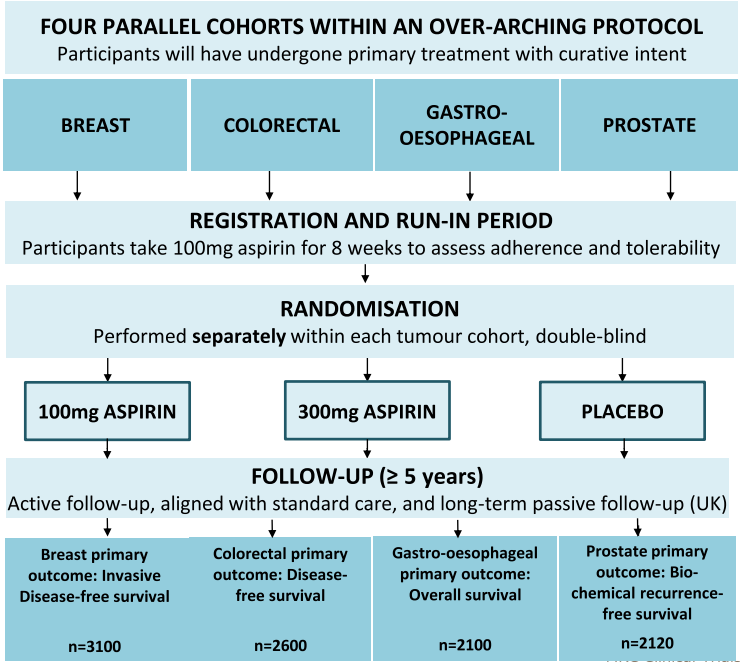

Fig 1. The Add-Aspirin trial.

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