MRC Clinical Trials Unit
Smarter studies
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Co-enrolment of participants into multiple clinical trials: The Add-Aspirin trial experience

Introduction

Opportunities to co-enrol participants into more than one cancer trial are not routinely considered. Benefits of co-enrolment have been identified in other settings and warrant exploration.

Add-Aspirin is a UK-wide trial assessing use of daily aspirin for preventing recurrence and improving survival following primary treatment for an early stage cancer (see schema opposite). Participants enter from a range of different treatment pathways across four tumour types. Co-enrolment opportunities have been pro-actively explored and managed.

Benefits and challenges of co-enrolment

A number of different interventions will be relevant to a patient over the course of their disease and treatment. As such, there are a number of potential advantages of co-enrolment which are widely applicable across multicentre oncology trials.

Potential benefits of co-enrolment include: improving recruitment feasibility; increased opportunities for patients to participate in trials; and collection of robust data on treatment combinations. The latter will ensure the ongoing relevance of individual trials and provide more cohesive evidence to guide management of future patients.

Perceived barriers to co-enrolment include scientific, safety and ethical issues. These warrant consideration on a trial-by-trial basis. Statistical and ethical issues are considered in the panels opposite.

Safety issues are highly dependent on the interventions. If there are concerns or a high degree of uncertainty about toxicity risks then co-enrolment is likely to be avoided. However, in a trial of a marketed product or intervention which is already in use in normal practice, co-enrolment will be more acceptable.

Factors affecting the potential impact of co-enrolment

Amount of co-enrolment	• Limited by extent of overlap in eligibility criteria and recruitment centres/period
Differential co-enrolment between arms of 1st trial	• May arise if differences in eligibility or willingness to participate • Difficult to predict – needs monitoring
Size of the effect of intervention*	• Modest effects expected in most phase III RCTs • Impact further limited if effects not seen for some time
Use of the intervention* outside of the trial	• Patients in first trial may receive intervention anyway • Not always relevant

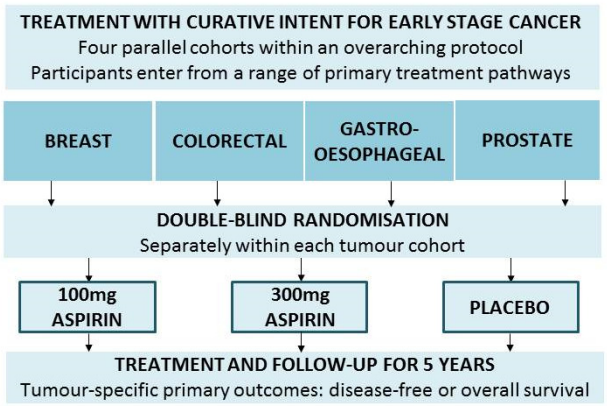
* Refers to the intervention being evaluated in the second trial (assuming sequential co-enrolment)

Managing co-enrolment

A number of measures for managing and monitoring co-enrolment within a trial are proposed (see table opposite). Engagement with participant representatives and PPI groups is vital to ensure that the approach is acceptable to participants and won't lead to unnecessary additional burden.

Since Add-Aspirin open in 2015, the potential to co-enrol has been agreed with more than 40 other trials across the 4 tumour types. 87/2422 (6%) participants have been co-enrolled and the proportion is similar across tumour types. The number joining from any one trial is small (<10), thus limiting any impact on those trials.

Add-Aspirin Trial Schema



Potential impact of co-enrolment on trial results

A principle concern with co-enrolment is the potential impact on the results of the trials, particularly when they are evaluating a common outcome measure.

Statistical modelling over a range of different scenarios has indicated that - in most cases - any impact on power is expected to be negligible, limited by a number of factors including the overlap of the trial cohorts (see figure opposite). However, this should be assessed on a trial-by-trial basis.

The participants' perspective

Trial co-enrolment will maximise opportunities for patients to participate in research. However, the approach must be ethically sound and acceptable to patients.

The potential to over-burden trial participants has been raised as a concern by some researchers, and this view has been a barrier to co-enrolment in other settings. Add-Aspirin participant representatives have been strong advocates of co-enrolment. They argue that there is an opposing ethical obligation to provide patients with information about any relevant trials, and allow them the autonomy to decide for themselves. This view is supported in the literature but studies are limited and further investigation with PPI (patient and public involvement) groups is warranted.

Proposed measures for managing co-enrolment in trials

	MEASURES FOR MANAGING CO-ENROLMENT
DESIGN	Identify where co-enrolment may be considered and assess potential impact and any safety issues; form agreements with other trial teams
	Engage PPI representatives/groups in discussions
	Develop consent process which will be acceptable to patients
	Ensure compatibility of follow-up schedules (and/or allow flexibility) to minimise extra visits
	Provide guidance on co-enrolment in the protocol (and trial website etc)
CONDUCT	Implement eligibility checks around co-enrolment
	Consider use of screening logs to flag issues
MONITOR	Collect and review co-enrolment information (including treatment allocation) on CRFs
	Establish agreements to share information between DMCs (blinded trials)

PPI – Patient and Public Involvement

Conclusions

Opportunities to enter patients into more than one 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.

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CANCER RESEARCH UK

NHS National Institute for Health Research