

# To co-enrol or not to co-enrol: that is the question

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The Declaration of Helsinki, now in its seventh revision,<sup>1</sup> provides a universal structure for medical research involving human subjects. Among the less known general statements of principle within that document are that “Medical progress is based on research that ultimately must include studies involving human subjects” and that “... interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality”.

Medical research may occasionally result in serious patient harm,<sup>2</sup> but there is some evidence<sup>3</sup> that, compared with regular patients, overall outcomes are at least as good for participants in research. Such a trial effect, if one exists, has been attributed to being treated by health care practitioners or institutions that take part in research.<sup>4</sup>

Medical research is essential for medical advances, but it is also evident that many of the more than 170 000 paediatric and adult patients admitted annually to Australian and New Zealand intensive care units<sup>5</sup> do not participate in any medical research leading to scientific publications.<sup>6</sup>

Low patient recruitment rates are an identified cause of unsatisfactory research in which patients are exposed to trial risks without the maximum possible gain in knowledge. Internationally, of more than 2000 registered clinical trials that closed in 2011, almost 20% terminated for failed accrual or completed with less than 85% of their expected enrolment, potentially compromising their statistical power.<sup>7</sup>

It may seem extreme<sup>8,9</sup> to adopt an ethical position that biomedical research is so important that there is a moral obligation to pursue it and to participate in it.<sup>10</sup> However, in practice, patients seem to consider medical research a high priority, with most reporting that they are in favour of personal trial participation, for altruistic reasons and potential personal benefit.<sup>11</sup> One described criterion for health care system excellence is that all patients who meet the selection criteria to participate in research are able to do so, if they desire.<sup>12</sup>

In the absence of widespread research participation, other strategies exist to study sufficient numbers of patients in clinical trials. Current clinical research most commonly uses parallel-groups designs,<sup>13</sup> with patients each receiving only a single therapy (patients nested within treatments). However, there is a long history of trial designs that deliberately expose some patients to more than one treatment, with this being the essential feature of factorial designs.<sup>14,15</sup> A simple balanced 2 × 2 factorial design has one-quarter of patients exposed to both active treatments concurrently.<sup>16</sup> In the absence of treatment interaction,

assessment of the independent effects of both treatments occurs with an efficient sample size. If there is interaction, the sample size advantage is lost, but an estimate of the magnitude of the effect modification (treatment interaction) is returned.

Other trial designs may also administer more than one therapy to research patients. Crossover trials are based on the administration of a sequence of treatments to every patient at different times to study within-patient differences; and re-randomisation designs, which allow each patient to be independently randomised on multiple occasions, may be applicable to some conditions for which patients will require treatment on several occasions.<sup>17</sup>

The enrolment of one patient into more than one study, when the patient fulfils all inclusion criteria and has no exclusion criteria for both studies (co-enrolment), is an increasingly common approach to augment patient clinical trial participation.<sup>18</sup> This practice has been incompletely studied,<sup>19</sup> but several critical care research groups have policies that offer selective support for the practice. Co-enrolment is feasible and does not overwhelm parents of paediatric patients, at least when they are faced with relatively low-risk trials.<sup>20</sup>

In this context, Reade and colleagues<sup>21</sup> are to be congratulated for directly addressing the reality of trial co-enrolment. 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 may be relevant to guide the management of future patients. There are also important ethical, safety, statistical and practical considerations,<sup>22,23</sup> and Reade and colleagues offer a checklist of items for consideration by trial management committees when assessing their own clinical landscape of potentially co-enrolling trials. It is no longer enough to ignore co-enrolment, allowing possible treatment interactions to occur in an uncontrolled and poorly evaluated fashion. Rather, potential bias and interaction should be considered, and co-enrolment should be specifically discussed in the scientific reports of each intervention.

The checklist of Reade and colleagues, together with other guidance on the important practical and statistical issues of co-enrolment,<sup>22-24</sup> elevate the importance of these issues for researchers.

In the 1980s and early 1990s, a rapid expansion in trials of multiple-drug therapies for HIV infection encountered complex co-enrolment statistical issues that did not fit with standard factorial designs, including potential interactions

among therapies applied at different times, possibly with competing risks.<sup>25,26</sup> Faced with clinical urgency to find effective therapies for HIV, researchers found that second study questions were arising after a first study had commenced, and some second studies focused on only a non-random subset of the first study, potentially inducing bias in conclusions.

There remains a strong place for traditional, parallel-group, randomised controlled trials testing a single intervention. However, in contemporary clinical research practice, it is likely that a strict “no co-enrolment” policy will often not be practical or efficient, so protocols should be designed to allow selected types of co-interventions to be identified, managed, assessed and reported. Collaborative standardisation of data collection with monitoring of withdrawal and adverse events will be important. Appropriate statistical analyses to explore potential treatment interactions, acknowledging a generally lower power to detect such interactions compared with main effects,<sup>22,26</sup> will enhance the scientific interpretation of overlapping clinical trials and their timely completion for the benefit of future patients. Co-enrolment is now an imperative for the intensive care community. Structuring, understanding and leveraging co-enrolment in the best possible way are important challenges for the future that must be met if we are to serve our patients’ interests at the highest level.

### Competing interests

None declared.

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