

# Considerations for co-enrolment in randomised controlled effectiveness trials in critical care: the SPICE-8 co-enrolment guidelines

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As investigators leading the Sedation Practices in Intensive Care Evaluation (SPICE) III clinical trial (NCT01728558), we are frequently asked by investigators in other studies whether we will allow co-enrolment. Thirty-four such requests were made in the 20 months before January 2017. The SPICE III trial is recruiting 4000 patients from 59 sites throughout Australia, New Zealand, Saudi Arabia, the United Kingdom, Ireland and Europe, and has very few criteria excluding early enrolment (< 12 hours of mechanical ventilation in the intensive care unit) of patients considered unlikely to be extubated the following day. Because of the need for early recruitment, enrolment in the SPICE III trial without the potential for co-enrolment could be a substantial impediment to other, equally valuable, research programs.

Co-enrolment increases research capacity, reduces the potential for selection bias that can occur if researchers must choose into which of several possible trials a patient will be enrolled, and appears to be acceptable to site investigators<sup>1</sup> and to patients and their relatives.<sup>2</sup> The empirical evidence suggests that co-enrolment according to sensible criteria does not influence patient safety or trial results.<sup>3,4</sup> We note that policy statements from several clinical trials groups,<sup>5,6</sup> including our own,<sup>7</sup> encourage co-enrolment into interventional trials. Pharmaceutical industry trials, however, commonly prohibit co-enrolment, which can present difficulties for research sites wanting to contribute to investigator-initiated collaborative research while also wishing (or needing) to participate in paid pharmaceutical trials.<sup>3</sup> The essential question to be answered when considering co-enrolment is whether it is likely to lead to conclusions in either of the two trials that would be different to those that would have been reached had the trials been conducted separately.

Our experience is that requests for permission to co-enrol almost never address the elements of scientific validity on which the advisability of co-enrolment rests. We have developed eight generalisable criteria by which we evaluate such requests, based on published empirical studies,<sup>3,4</sup> theoretical arguments,<sup>8</sup> opinion surveys<sup>1</sup> and the guidelines of others.<sup>5-7</sup> We hope dissemination of these eight criteria (summarised in Table 1) will facilitate more efficient assessment of requests for co-enrolment in other critical care effectiveness trials, and ultimately allow greater

## ABSTRACT

- The Australian and New Zealand Intensive Care Society Clinical Trials Group and other investigator-led trials groups in critical care publish policies and guidelines outlining the rationale for considering co-enrolment in large, randomised controlled trials in intensive care medicine. However, none present a checklist of criteria by which a request for permission to co-enrol in an existing trial can be assessed.
- Consequently, such requests tend to be made and assessed on an ad hoc basis. Based on our experience in the SPICE III randomised controlled trial, we propose eight broadly applicable criteria (the SPICE-8 criteria) to be satisfied before co-enrolment should be approved.
- Reporting co-enrolment in trials, for regulatory purposes and in publications, is uncommon, partly because of the complexity involved in explaining a lack of a plausible co-enrolment effect. We suggest that noting compliance with these criteria would simplify such reporting and enhance transparency.

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capacity to conduct scientifically valid critical care research. These criteria are framed from the perspective of a new trial (Trial B) seeking permission for co-enrolment with one that is already underway (Trial A); this is the most common situation. We will not consider the appropriateness of testing interventions in factorial trial designs, other than to note that these are essentially co-enrolling studies harmonised to operate within one experimental protocol and so are subject to similar criteria to those outlined here.

## Scientific considerations

**1. There should be little or no biological interaction between the interventions or, if there is a possible interaction, there is little difference to what would have been standard care.**

There should be little or no plausible biological interaction between the experimental interventions in the two trials. For example, in our trial of a dexmedetomidine-based sedation

**Table 1. The SPICE-8 criteria that must be considered in assessing whether co-enrolment in a proposed trial (Trial B) should be allowed for patients already enrolled in a trial that is underway (Trial A)**

Criterion	Description
Biological interaction between interventions	There should be little or no plausible biological interaction between the experimental interventions in the two trials; <i>or</i> If there is a potential biological interaction, the interventions in Trial B would have been received by the patients in Trial A in approximately the same proportions, had they received only routine clinical care rather than that provided because they were enrolled in Trial B.
Effects on protocol compliance and intercurrent care	There should be little likely influence on Trial A protocol compliance or intercurrent care resulting from enrolment in Trial B.
Equal allocation to trial groups	The treatment groups in Trial A should have equal chances of being allocated to the treatment groups in Trial B.
Treatment restrictions	Any protocol-mandated treatment restrictions in the intervention or control group of Trial B should not alter the treatment of either group in Trial A.
Mandated intercurrent treatments	Intercurrent treatment requirements in the control or intervention groups of Trial B should not substantially alter the treatments of patients in Trial A.
Outcome ascertainment	Ascertainment of outcomes in Trial B should not affect the outcomes in Trial A.
Clinical decision making	Information collected in Trial B that would not otherwise have been collected, and that is contemporaneously available, should not alter clinician decision making in any way that might affect the interventions, intercurrent care or outcomes of Trial A.
Adverse event procedures	The procedure for dealing with an adverse event in Trial B should not have an impact on the conduct of Trial A.

protocol, it would be inappropriate to co-enrol patients in a trial of a novel sedating opioid, but acceptable to co-enrol patients in a trial of proton-pump inhibitors.

If there is potential for a biological interaction between the experimental interventions in the two trials, there should be a reasonable expectation that the interventions in Trial B would have been received by the patients in Trial A in about the same proportions as if they had received only routine clinical care, rather than the care provided because they were enrolled in Trial B. For example, a trial comparing central neuraxial versus peripheral regional analgesia for a particular type of surgery (with 1:1 randomisation) might be acceptable to the SPICE III investigators for co-enrolment if about 50% of SPICE III patients would have received treatment using each of these two modalities as part of their intercurrent care. However, as 50% of the SPICE III trial patients receive dexmedetomidine (a less commonly prescribed sedative outside the trial context), investigators in the regional analgesia trial would be unwise to request co-enrolment with the SPICE III trial. In this circumstance, it might be acceptable for patients in the usual-care arm of the SPICE III trial to be eligible for randomisation in the regional analgesia trial, as long as all other criteria listed were met.

## 2. There should be little likely influence on Trial A protocol compliance or intercurrent care resulting from enrolment in Trial B.

The potential interaction between treatments in Trial A and Trial B is not limited to biological effects, but includes delays

in receiving prescribed trial or intercurrent therapy, the number of clinicians caring for the patient, or the location in which they will be nursed. Consequently, there should be little likely influence on Trial A protocol compliance or intercurrent care resulting from enrolment in Trial B. For example, if Trial B is a process-of-care intervention that results in greater clinician attention to some patients, these patients might plausibly have the two sedation protocols in the SPICE III trial implemented differently.

## 3. Ideally, the treatment groups in Trial A should have equal chances of being allocated to the treatment groups in Trial B.

This is not essential if there is no possibility of interaction between the two treatments and intercurrent care is the same in both trials, but this would rarely be the case. For example, if Trial B has a 1:2 randomisation schedule, there must be no chance that the intervention or intercurrent care in Trial B could affect the outcomes of Trial A.

## 4. Any protocol-mandated treatment restrictions in the intervention or control group of Trial B should not alter the treatment of either group in Trial A.

Usually, certain treatments (such as the experimental treatment) would be prohibited in the control group of any trial. Such prohibition is only acceptable to Trial A if this treatment is not in common clinical use, or if it could not plausibly affect the outcome of Trial A. For example, prohibition of the use of regional analgesia in Trial B would make co-enrolment in the SPICE III trial impossible, but

prohibition of an uncommonly prescribed antibiotic, when alternatives are available, would be acceptable.

### **5. Intercurrent treatment requirements in the control or intervention groups of Trial B should not substantially alter the treatments of patients in Trial A.**

For example, in the SPICE III trial, it would not be appropriate to co-enrol patients in a study that protocolises ventilator weaning and extubation, because time to extubation is one of the endpoints of the SPICE III trial.

### **6. Ascertainment of outcomes in Trial B should not affect the outcomes in Trial A.**

For example, a study that required frequent blood sampling overnight could plausibly interrupt sleep patterns, potentially affecting the outcomes of the SPICE III trial.

### **7. Information collected in Trial B that would not otherwise have been collected, and that is contemporaneously available to clinicians, should not alter clinician decision making in any way that might affect the interventions, intercurrent care or outcomes of Trial A.**

For example, a study that mandated intracranial pressure monitoring might reveal information that would influence the prescription of sedatives in the SPICE III trial, making this study unsuitable for co-enrolment. Another more common example might be a Trial B that mandated regular blood tests in excess of those ordinarily performed for clinical purposes, the results of which might affect treatment in Trial A.

### **8. The procedure for dealing with an adverse event in Trial B should not affect the conduct of Trial A.**

There should be a plausible expectation that the outcomes of Trial A should not be affected by any adverse outcomes in Trial B any more than would be the case with expected complications of standard intercurrent care. Specifically, discontinuation of a Trial B treatment, or therapy for a complication, should not affect the patient continuing in Trial A. This would generally preclude trials of novel investigational products in patients enrolled in large effectiveness trials, such as the SPICE III trial, because drugs in early-phase development usually have, by definition, uncertain adverse effect profiles.

## **Effects of treatment interactions**

A detailed simulation analysis of the effect on two co-enrolling trials testing interventions that interact has been performed,<sup>8</sup> but we recommend that this possibility only be entertained in compelling and unusual circumstances (eg,

when it is important to understand the nature of the drug interaction), in which case a single-factorial trial design is likely to be more appropriate.

## **Interactions with observational studies**

The above discussion is framed in the context of a second randomised controlled trial of an intervention asking to co-enrol with an existing trial. In general, there is less concern about patients enrolled in an interventional trial being simultaneously enrolled in a prospective observational study, as there is no possibility for interaction with another intervention. However, the considerations listed above in points 2, 6 and 7 would be relevant, and a request to co-enrol into such a study should address these.

## **Study power considerations**

A potential disadvantage of co-enrolment can occur if two large, pragmatic effectiveness trials with similar outcomes enrol the same patients. If the intervention in Trial B results in a substantial improvement in the common outcome (eg, in 90-day mortality), even if there is no biological interaction between Trial A and B treatments, the potential for Trial A to show benefit is reduced.<sup>7</sup> In practice, treatment effects are rarely so great as to make this an important consideration. Consequently, this does not form one of our recommended criteria.

## **Practical considerations**

Obtaining consent for trial participation can be onerous for patients, relatives, research staff and clinicians. We believe that participating trial sites should assess, ideally on an individual patient basis, whether the burden of gaining consent for more than one study approved for co-enrolment outweighs the benefit to the research capacity of the ICU. The burden of seeking consent for a second or subsequent trial may be particularly great in situations where a patient has already been enrolled in a study exempted from the requirement for prospective consent. Investigators should take into account the decision-making ability of the patient or their relative and the nature of the clinician–patient relationship that has developed. If it is decided that consent for only one of several available trials will be sought, site investigators must ensure that the potential for recruitment bias is minimised. For example, the trial chosen should not be the one that attracts the greatest reimbursement, the one with the most straightforward consent and data collection, the one with the earliest mandated recruitment window, or the personal project of one of the site investigators. Ideally, the trial to be allocated priority for a patient should be chosen at random. Alternatively, irrespective of trial

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management committee decisions on co-enrolment, sites with insufficient resources to co-enrol in two trials might choose to participate in only one, to minimise recruitment bias.

If possible, trials that co-enrol patients should collect harmonised data modules to increase efficiency of data collection. In principle, the SPICE III study would share patient baseline, treatment and outcome data with other trial groups that required identical data for patients co-enrolled in their study. This would require such groups to accept the content and integrity of data that would be beyond their control, which perhaps explains why there are few, if any, examples in the critical care literature of this occurring.

### Reporting co-enrolment

A decision to permit co-enrolment is, arguably, a modification to the trial protocol. If so, each decision should be communicated as a protocol amendment to each site human research ethics committee (HREC). This would be a burdensome administrative task that, not surprisingly, seldom occurs in practice. Our recommendation is that trial protocols should contain a clause noting that the management committee can approve, without further HREC review, co-enrolment into any trial that meets certain published criteria, such as those outlined in this article. Similarly, it is not common practice to report in articles reporting trials whether co-enrolment has been permitted during the conduct of the study. We recommend that potential uncertainty could be resolved by reporting, without further detail, that co-enrolment with other trials that met these published criteria was allowed.

### Empirical testing

Evidence-based medicine requires testing of even the most compelling theoretical arguments. Here, we have described eight co-enrolment conditions based on theoretical considerations alone. Several studies have found that whether or not co-enrolment occurs is associated with patient and trial characteristics (eg, illness severity, experience of the person seeking consent and hospital size),<sup>3,4</sup> but no study has shown an association with trial outcome. However, the effect of co-enrolment in trials that meet, or do not meet, criteria such as those we propose has never been tested. Such a study might be possible if investigators were to note co-enrolment in their case report forms, and agree to share these and all other individual patient data.

Collaborative groups performing several studies simultaneously, such as the Australian and New Zealand Intensive Care Society Clinical Trials Group, could facilitate this within a governance structure that preserves the integrity of individual trial datasets. Testing the absence of co-enrolment effect in studies meeting the proposed criteria would then be possible. Assessing studies at theoretical risk of interaction would most likely be hampered by investigators' lack of willingness to co-enrol in such studies. Nonetheless, we suggest that trials should record every instance of individual patient co-enrolment to facilitate future testing of these criteria.

### Conclusion

We propose these eight "SPICE-8" criteria as the elements that must be evaluated by trial groups requesting or considering co-enrolment with large, multicentre, effectiveness clinical trials. Our intent is that this will reduce much repetitive discussion, encourage collaboration and facilitate transparency, while reducing governance burdens, and will ultimately increase the research capacity within clinical intensive care medicine.

### Competing interests

None declared.

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