

## Co-Enrolment Policy

### Scope

Co-enrolment refers to the enrolment of an individual patient concurrently into two or more clinical trials, including both interventional and observational studies. This policy covers both CTG endorsed studies and other clinical trials, including interventional and observational studies and should be read in conjunction with the CTG Competing Studies Policy.

### General Principles

1. ANZICS-CTG encourages co-enrolment into research trials, including those conducted by intensive care researchers and from other clinical areas according to the principles outlined in this document. This policy provides guidance to researchers and study management committees on the issues that should be addressed when considering co-enrolment.
2. The primary concern of the researcher must remain the patient for whom – directly or indirectly – the researcher and the intensive care unit provide clinical care.
3. Discussion must occur between investigators undertaking research which involves interdepartmental boundaries to determine barriers to co-enrolment and procedures to follow when patients are co-enrolled.
4. There may be an obligation on investigators to offer co-enrolment and opportunity to participate and therefore all potential therapeutic benefits of more than one study to patients.
5. All potential interactions between studies should be considered before patients are enrolled into more than one study.

### Implications of co-enrolment for Intensive Care Research

Potential advantages of co-enrolment include:

1. Ability to increase the throughput of clinical trials allowing results of potentially beneficial interventions to be available earlier.
  - a. Faster completion of individual trials.
  - b. Ability to run more trials concurrently
2. Efficiency savings from consent and data collection processes
3. Avoiding selection bias in allocating patients to specific studies:
  - a. If co-enrolment is not permitted, patients may be allocated to a particular study based on factors such as perceptions about study design, study progress or remuneration.
  - b. If a study of a particular patient group doesn't allow co-enrolment with a concurrent study of "ICU all-comers" the latter may not be able to adequately reflect the patient population it is targeted at.
4. Reducing the potential for conflict between groups of researchers seeking to enrol the same population of patients into different clinical trials.
5. As participation in clinical trials for intensive care patients is common, permitting co-enrolment best reflects a truly pragmatic approach to study design.

Potential disadvantages include;

1. Weakening of power of the study, especially if a large proportion of patients are enrolled into 2 (or more) studies with the same outcome and anticipated same direction of effect (e.g. reduction in 90 day mortality).
2. Bias due to interaction between the interventions being studied leading to a misleading increase or decrease of observed effect.
3. A perception of “overburdening” patients or surrogate decision makers. There is little support from the literature for this (and some support for the opposite).

### **Specific Issues**

When determining whether or not to permit co-enrolment Principal Investigators and Management Committees should consider:

- The effect of co-enrolment on the design and scientific integrity of the study, including sample size calculations.
- The implications on refusal to allow co-enrolment on both their own and other studies being undertaken concurrently in the same patient group.
- The impact of co-enrolment on the patient and their family, with particular regard to consenting and follow up procedures.
- The implications of co-enrolment on research coordinator workload.

### **Study design and statistical considerations**

It is important that the implications of co-enrolment are considered during the design stage of clinical trials. Consideration should be given to the potential for an effective intervention in a simultaneous study to change the baseline frequency of a measured variable and also to potential interactions between the interventions being studied. Interaction is not limited to direct physiological or pharmacological effects and potentially includes differential enrolment into the second trial on the basis of the first, altered timecourse in receiving each intervention and the changes to the processes of care delivered.

Factorial study design should be considered for studies with a similar patient population and timeframe to improve efficiency or to specifically investigate interaction. The use of different outcome measures in two trials does not eliminate the potential for interaction if one is on the causal pathway to the other.

### **Implications on the feasibility and recruitment rate of trials**

Anticipated recruitment rates may not be met if a competing study does not allow co-enrolment or if the burden of multiple trial participation reduces the number of subjects who agree to be part of the study. For intensive care researchers earlier access to the patients by other research groups (including cardiology, anaesthesia and surgery) may limit the number of patients who can be enrolled subsequently. It is recommended that intensive care researchers discuss the implications of other studies that do not permit co-enrolment at the earliest opportunity.

## Patient participation and Consent

Consideration should be given to both the timing of the provision of information to patients/surrogate decision makers. Concern has been expressed about the extra burden being put on patients and surrogate decision makers by being approached for consent to be enrolled in multiple studies, although the literature does not support these concerns. Researchers should ensure that the information provided to participants allows them to adequately assess the different studies available. Where possible, information on the breadth of research being performed in ICU should be provided to patients and their families at the earliest opportunity.

Although there may not be one “best approach” to gaining informed consent for participation in more than one study, if patients are eligible for inclusion in more than one study, researchers should determine which study to approach them or their family/substitute decision maker with first. This may need to be done bearing in mind study requirements around timely enrolment.

## Research Coordinator and Data Collection Implications

Wherever possible, data collection tools and processes should be standardised across studies to facilitate efficient collection of data;

- Standardised and/or modular CRFs may improve efficiency of data collection e.g. SAE forms; lab results
- Standardisation of data collection schedule and 24 hour period
- Coordinated patient follow up – including clinic visits and phone calls.

This would assist in reducing any burden of workload for research coordinators, study participants and their family. It may be prudent to identify co-enrolled patients on CRFs and to detail the extent of co-enrolment when reporting study results.

## Resources

1. Angus, D., Mira, J.-P., & Vincent, J.-L. (2010). Improving clinical trials in the critically ill. *Critical Care Medicine*, 38(2), 527 - 532.
2. Cook, D. J., Blythe, D., Rischbieth, A., Hebert, P. C., Zytaruk, N., Menon, K., . . . Meade, M. O. (2008). Enrollment of intensive care unit patients into clinical studies: a trinational survey of researchers' experiences, beliefs, and practices. *Critical Care Medicine*, 36(7), 2100-2105. doi:10.1097/CCM.0b013e31817c00b0
3. Golec, L., Gibbins, S., Dunn, M. S., & Hebert, P. (2004). Informed consent in the NICU setting: an ethically optimal model for research solicitation [Review]. *Journal of perinatology : official journal of the California Perinatal Association*, 24(12), 783-791. doi:10.1038/sj.jp.7211198
4. Morley, C. J., Lau, R., Davis, P. G., & Morse, C. (2005). What do parents think about enrolling their premature babies in several research studies? *Archives of disease in childhood. Fetal and neonatal edition*, 90(3), F225-228. doi:10.1136/adc.2004.061986
5. Nichol, G., Powell, J. L., & Emerson, S. (2010). On coenrollment in clinical resuscitation studies: review and experience from randomized trials. *Resuscitation*, 81(7), 792-795. doi:10.1016/j.resuscitation.2010.03.014
6. Randolph, A. G. (2009). The unique challenges of enrolling patients into multiple clinical trials. *Critical Care Medicine*, 37(1 Suppl), S107-111. doi:10.1097/CCM.0b013e3181921c9d