Co-enrollment Guidelines for Interventional PICU Studies

Background

Co-enrollment is the concurrent enrolment of 1 patient into more than one study. Both scientific factors (e.g. unrelated trial interventions) and psychosocial factors (e.g., family dynamics) influence the decision to offer co-enrolment to critically ill patients and/or substitute decision maker (SDM). Today in the PICU, as in other settings, co-enrolment is occurring with a variety of paired study designs (such as 2 observational studies, 1 RCT and 1 observational study, or 2 RCTs).

Possible advantages of co-enrolment of 1 patient into 2 RCTs include the opportunity for research questions to be answered more quickly, the chance for research coordinators to be more efficient by collecting 2 (often overlapping) datasets on 1 patient, the chance that patients may receive better care while enrolled in a second trial, the chance that patients in a trial, in general, may have better outcomes than similar patients enrolled in one trial, the opportunity for patients and/or SDMs to contribute more to new knowledge, and the opportunity for patients and/or SDMs to have additional supportive contact and follow-up with members of the research team. Evidence supports that parents are willing to have their children participate in multiple studies (1). Possible disadvantages of co-enrolment of 1 patient into 2 RCTs include a scientific interaction of the interventions (for example, attenuation of a true treatment effect from one intervention induced by the second intervention), rendering the contribution of that patient to both trials questionable. Each co-enrolled patient could have an increased probability of adverse events by being enrolled in 2 rather than 1 trial. There is a possible consent burden for the patients and/or SDMs, and increased workload for the research team on a per patient basis.

Overall, co-enrollment was viewed as an effective, feasible and ethical means to increase enrolment of critically ill patients into studies and RCTs. Since co-enrollment is ongoing in many disciplines today, little is known about it, and REB involvement is variable, we have adopted the guidelines developed by Cook DJ et al in collaboration with the CCCTG(2).

The McMaster Children's Hospital PICU supports the participation of a patient in multiple observational and/or interventional studies. However, there are specific considerations when co-enroling a patient into more than one ***interventional*** study or trial. The PICU research committee supports co-enrollment into more than one interventional study or clinical trial, provided the following considerations are fulfilled:

Scientific Issues:

- In the event that co-enrolment is considered of 1 PICU patient into 2 or more interventional studies/trials:
    - Interventions being tested in the RCTs are commonly available interventions (e.g., we recommend against co-enrolment for new biologicals or devices for which mechanisms and outcomes are very uncertain).
    - Evidence for potential for biologic or mechanistic interaction in the interventions tested in RCTs under consideration for co-enrollment have been reviewed and discussed amongst the investigators of both trials.
    - Stakeholders are in agreement: i.e. the Principal investigators, RCT Steering

- Committees and PICU Research Committee

- The Canadian Critical Care Trials Group (CCCTG) is in agreement, for relevant CCCTG trials.

Consent Issues:

- The research coordinator is aware of the co-enrollment plan so that the approach to more than one consent is sensitive and scientifically sound.
- The patient and/or SDM appears to be coping with decision-making responsibilities
- The dynamics between the patient and/or SDM and PICU team are appropriate for ongoing research opportunities to be presented.
- The patient and/or SDM gives free and informed consent to enroll in each study respectively (unless the study has waived consent).

Context Issues:

- Co-enrolment is possible considering the workload of the research coordinator
- The PICU attending is in agreement (so that consent withdrawals are minimized)
- Co-enrolment is permitted as per local REB policy.

Documentation Issues:

- Plans to coenrol 1 patient into 2 RCTs are submitted and approved by the local REB before recruitment into each RCT begins, with provisos as noted above.
- Patients screened and approached for co-enrolment are documented, and consent rates for co-enrollment are documented
- All parties involved with the patient's care (health care providers and caregivers) will be informed of the patient's/SDM's consent to participation in one or more studies.
- The foregoing reports are submitted periodically to each RCT Steering Committee and the appropriate stakeholders as described above (and the local REB if they are interested/request this information).
- A guideline (such as this), policy or Standard Operating Procedure (SOP) is developed and approved at participating sites by relevant stakeholders.

Approach:

1) Co-enrollment checklist – the checklist for co-enrollment into 2 or more interventional studies/trials should be completed and reviewed by the PICU research committee to determine appropriateness of co-enrolment (see Appendix 1: Co-enrolment Checklist)

2) Communication:

a. Upon admission, at the appropriate time, caregivers and patients will be given information package that this is an academic institution with a rich culture and tradition of research and quality improvement. They will be informed of a number active ongoing

studies in the PICU and the possibility that they will be approached for one or more of these studies on ongoing basis.

b. Research teams for each study should work together to facilitate co-enrollment and optimal communication regarding each study e.g:

- The communication strategy to stakeholders and PICU health care providers regarding ongoing studies
- Contact person(s) for each study
- Screening mechanism for each study
- Where possible, the same team should approach for both trials if they already have a rapport with the parents, so that caregivers are not meeting too many new faces (see below)
- The outcome of consent discussions should be shared amongst the teams – e.g. if the SDM declined consent for a study clearly states that they do not want to take part in any kind of research, they will not be approached for a second study

3) **Simultaneous consent:** Where possible, in order to reduce the burden to SDMs and patients with decision making responsibilities during the critical illness, there will be a combined approach to co-enrolment, if there is one patient who is simultaneously eligible/potentially eligible for more than one study or RCT at the time of screening (i.e. overlapping enrolment window). Where possible, the same team should approach for both trials if they already have a rapport with the parents. Where possible, the studies may be presented as a package (e.g. "Sepsis trials", or "Transfusion trials"), and the approach to co-enrollment will be built into the procedure manual and or protocol for each respective study. Priority will be given to given to studies lead by investigators at the McMaster site.

4) Overlapping Enrolment Window, randomization and timing of Intervention:

The process of co-enrollment should *not* threaten the window for screening, enrolling and administering the intervention for the respective study or studies under consideration. Adherence to each respective study protocol and procedures should be strictly observed.

5) **Special considerations**:

When approaching for co-enrollment, priority will be given to given to studies lead by investigators at the McMaster site. i.e. Informed consent procedures of potential studies under consideration for co-enrollment will prioritize presenting studies lead by investigators at McMaster.

- *Deferred consent:*

  When deferred consent and SDM consent are both permitted for study inclusion, the outcome of the deferred consent will be clarified first prior to approaching for co-enrollment into additional study(s).

  When deferred consent is permitted for more than one study inclusion, priority will be given to studies lead by investigators at McMaster Children's Hospital.

- *Telephone consent*

In person consent if preferred when approaching for co-enrollment. When approaching for co-enrollment over the telephone, we suggest that an agreed upon script be followed, in line with item # 2 above

Acknowledgements:

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Reviewed and approved by: The PICU Research Committee members and member of the PICU Division, McMaster Children's Hospital

References:

1. Morley CJ, Lau R, Davis PG, Morse C: What do parents think about enrolling their premature babies in several research studies? *Arch Dis Child Fetal Neonatal Ed* 2005, 90:F225-228.
2. Cook D, Hebert PC, Zytaruk N *et al*: Enrolment of 1 ICU patient into 2 Randomized Trials. Guidelines of the CCCTG, 2007.
3. Cook D, McDonald E, Smith O *et al*: Co-enrollment of critically ill patients into multiple studies: patterns, predictors and consequences. *Critical care* 2013, 17:R1.
4. Harron K, Lee T, Ball T *et al*: Making co-enrolment feasible for randomised controlled trials in paediatric intensive care. *PloS one* 2012, 7:e41791.
5. D Cook, E McDonald, F Clarke, L Hand et al. Enrolment of 1 Adult ICU Patient into 2 RCTs. St. Joseph's Health Care Hamilton Guidelines, May 18 2008.

McMaster PICU Research Co-enrolment checklist.

Objective: guide to determining appropriateness of co-enrollment into 2 or more *interventional* studies/trials.

	Study A	Study B
Study:		
Scientific Issues		
Intervention tested is commonly available (recommend against co-enrolment for experimental intervention for which mechanisms and outcomes are very uncertain)	☐Yes ☐ No	☐Yes ☐ No
Interventions unrelated or unlikely biologic/mechanistic interaction	☐Yes ☐ No ☐ Unknown	☐Yes ☐ No ☐ Unknown
Co-enrollment is not a contraindication to eligibility	☐Yes ☐ No	☐Yes ☐ No
Stakeholders are in agreement with co-enrollment (e.g. PI, Steering Ctee., REB, CCCTG, MRP group)	☐Yes ☐ No	☐Yes ☐ No
Context and Consent Issues:		
Co-enrolment permitted by local REB policy	☐Yes ☐ No	☐Yes ☐ No
Consent issues and considerations have been discussed by PI's of each study	☐Yes ☐ No	☐Yes ☐ No
Screening and co-enrolment can be operationalized by research staff	☐Yes ☐ No	☐Yes ☐ No
SOP available for operationalizing co-enrolment in each study, in accordance with PICU co-enrollment guidelines	☐Yes ☐ No	☐Yes ☐ No
Research staff trained on SOP for co-enrollment	☐Yes ☐ No	☐Yes ☐ No
Clear information package available for SDM/patient explaining each study and possible impact of co-enrolment	☐Yes ☐ No	☐Yes ☐ No
Reviewed by PICU Research Committee:	☐Yes Signature: _____ Review date: __/__/____	
Recommendations: (Consider suitable for co-enrollment if answered "Yes" to all items where appropriate) **Comments:**	☐Yes ☐ No	☐Yes ☐ No