Enrolment of 1 ICU Patient into 2 Randomized Trials

Guidelines of the CCCTG, 2007

Background

Clinical research is key to the future of improved clinical care in the ICU. Reducing the morbidity and mortality of critical illness requires a broad clinical research agenda to understand how to reduce organ dysfunction, improve survival, restore health and maximize quality of life. However, the conduct of clinical research in the ICU setting involves unique challenges. Data collection can be complex and expensive. The vulnerability of critically ill patients raises concern about patient safety during research, underscoring the need for careful research oversight. Experimental interventions may cause more harm than good, or introduce risk with no benefit. The need to begin some interventions rapidly means that enrolment is often time-sensitive, straining the consent process. However, most patients in the intensive care unit (ICU) have no decision-making capacity due to their underlying condition or medications they receive. Since first person informed consent is rarely possible for critically ill adults or children, consent is usually sought from legal substitute decision makers (SDMs) who are often under considerable duress. Practitioners, investigators, funding agencies, regulatory authorities and the public recognize that these concerns must be balanced by the need to undertake clinical research in the critically ill, to seek scientific advances that will improve the outcomes of these patients.

If a patient is eligible for enrolment in 2 or more randomized clinical trials (RCT), research personnel may elect to approach the patient and her/his SDM for enrolment in 1 RCT. Several factors could influence the choice of which RCT is pursued by the research team, including perceived differences in the merits of the 2 trials (methodologic rigour, risk for harm, or likelihood of benefit), political considerations (whether the RCT is investigator-initiated, or whether it is a local investigator-led RCT, or a trials group RCT), or practical influences (trials with more generous remuneration may be favoured, those which are administratively easier to conduct, or those which help to fulfill recruitment quotas).

Co-enrolment is the enrolment of 1 patient into 2 studies. Both scientific factors (e.g., unrelated trial interventions) and psychosocial factors (e.g., family dynamics) influence the decision to offer co-enrolment to SDMs of an ICU patient. In critical care, as in other disciplines, co-enrolment is occurring with a variety of paired study designs.

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 sets of data 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 their SDMs to contribute more to new knowledge, and the opportunity for SDMs to have additional supportive contact and follow-up with members of the research team. Possible disadvantages of co-enrolment of 1 patient into 2 RCTs include a scientific interaction of the interventions 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 SDM, and increased workload for the research team on a per patient basis.

Since data are sparse on professional and public views towards co-enrolment of 1 critically ill patient into 2 RCTs, we undertook an initial survey in 2007 to understand the experiences, beliefs and practices of physician and research coordinator members of the CCCTG and ANZICS-CTG regarding enrolment of critically ill children and adults into clinical

studies. We reasoned that a better understanding of enrolment strategies as viewed by research personnel would inform us in further developing the design and conduct of clinical investigations in critical care.

Overall, co-enrolment was viewed as an effective, feasible and ethical means to increase enrolment of ICU patients into RCTs. Half of the 284 respondents have already adopted co-enrolment with scientific and psychosocial provisos in 2007. In centers participating in the CCCTG, 11% of respondents reported that their local REB had a guideline or policy and 35% reported that there was a local ICU 'rule of thumb' or policy in the ICU or REB. The limited policies that existed were variable including: endorsement of co-enrolment providing that the scientific integrity and ultimate interpretation of either RCT is not jeopardized; enrolment in a maximum of 2 RCTs; allowance of 1 RCT and 1 or more observational studies; no restrictions; or prohibition of co-enrolment. These ICU policies included pursuing co-enrolment as long as the decisional burden does not appear too high, as long as the attending ICU physician agrees, and if consultation with the local REB allows it, on a case-by-case basis.

Since co-enrolment is ongoing in many disciplines today, and little is known about it, and since there is great REB variability, we developed draft guidelines. The following guidelines refer primarily to co-enrolment of 1 patient into 2 RCTs of established interventions (not to co-enrolment in industry-initiated RCTs or into trials of new drugs or devices).

2C Guideline Recommendations

We suggest considering coenrolment of 1 ICU patient into 2 RCTs only if
Scientific Issues:

- Interventions being tested in the 2 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).
- The intervention arms are unrelated and there is unlikely to be biologic interaction in the interventions tested in the 2 RCTs.
- Both of the RCT Steering Committees are in agreement.
- The CCCTG is in agreement.

We suggest considering coenrolment of 1 ICU patient into 2 RCTs only if
Consent Issues:

- The SDM appears to be coping with decision-making responsibilities
- The dynamics between the SDM and ICU team are stable.
- The SDM gives free and informed consent.

We suggest considering coenrolment of 1 ICU patient into 2 RCTs only if
Context Issues:

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

We suggest considering coenrolment of 1 ICU patient into 2 RCTs only if
Documentation Issues:

- Plans to coenrol 1 patient into 2 RCTs are submitted and approved by the local REB before recruitment into each RCT begins.
- Patients screened and approached for co-enrolment are documented, and consent rates for coenrolment are documented.
- The foregoing reports are submitted periodically to each RCT Steering Committee and the CCCTG (and the local REB if they are interested).

Guideline Update Plans

Studies published to date are only the beginning of the work needed on this topic. These guidelines will be updated as new evidence emerges and ethical analysis is refined.

Future Research

- Further empiric work, scientific discourse and ethical analyses are needed on co-enrolment in the ICU, given that is ongoing and increasing, in several countries for pediatric and adult critical care.
- Input is needed from other stakeholders such as citizens, patients, SDMs, and REBs.
- Surveying other respondent groups would be useful, including clinicians working in ICUs that do clinical research, clinicians working in large ICUs that do not conduct research, clinicians working in smaller ICUs, and clinicians in other countries.
- In addition to surveys, observational research and interventional studies are needed on the consequences of co-enrolment from several perspectives.

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