Co-enrolment for the TAME and TTM-2 trials: the cerebral option

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Out-of-hospital cardiac arrest (OHCA) is a major health problem — a common and catastrophic event. In Australia, the annual incidence of OHCA is one per 1000 people. Survival rates are low, and many survivors experience cognitive impairment.[1-3] Even among the 39% who arrive at hospital alive,[4] about 40% survive to hospital discharge.[5,6] The predominant cause of death after hospital admission is brain injury and, for patients who survive, there is a high incidence of neurological injury, ranging from cognitive impairment to permanent severe disability.[7] The disabling effects of neurological injury after cardiac arrest persist for many years, and the human and financial costs of supporting survivors are substantial.[8,9] Prevention of secondary neurological injury is a key priority in the management of resuscitated patients after OHCA once they arrive in the intensive care unit. Currently, only about 30% of patients who survive a cardiac arrest leave hospital with good neurological function.[10] Further improvements in care may lead to improved survival, better recovery and substantial cost savings for individuals and health systems.

Further improvement in outcomes for survivors of OHCA requires rapid advances in research efforts directed at evaluating interventions that are most likely to lead to improvements in survival and patient-centred outcomes. These interventions have been identified as a priority for this patient group.[11] Clinical research requires dedicated individuals who are able to not only develop the trials but also to obtain the funding required, lead the trials, enrol the patients and collect the data.

Multicentre, international randomised controlled trials involving critically ill patients are not a new initiative. Many recent landmark trials in this patient population (the ARISE, NICE-SUGAR, RENAL, DECRA and EPOTBI trials) have relied on international collaboration to complete enrolment and ensure greater external validity of results.

Two global trials of different interventions aimed at mitigating the effects of OHCA on neurological function are planned to commence enrolment this year: the Hypothermia or Normothermia-Targeted Temperature Management After Out-of-hospital Cardiac Arrest (TTM-2) trial and the Targeted Therapeutic Mild Hypercapnia After Resuscitated Cardiac Arrest (TAME) trial. Both trials plan to enrol patients admitted to the ICU after OHCA and follow on from previous work by both groups.[7,12]

Both trials have appropriately large sample sizes, necessitating international collaboration to achieve adequate recruitment rates and obtain the necessary funding. TAME aims to assess whether targeted therapeutic mild hypercapnia ($Paco_2$, 50–55 mmHg) improves neurological outcome at 6 months compared with standard care ($Paco_2$, 35–45 mmHg). TTM-2 tests the hypothesis that targeted hypothermia (33°C) reduces mortality 180 days after OHCA and improves neurological function, compared with targeting normothermia if fever > 37.7°C occurs.

Importantly, these trials are pragmatic because the interventions are, in the case of therapeutic hypercapnia, cost-free and simple to apply. Findings may improve the lives of thousands, transform clinical practice and yield major economic gains worldwide.

Having two trials in process in the same space in a limited patient population offers significant challenges with respect to competitive recruitment and research capacity at sites. However, it also offers a unique opportunity for harmonisation of study procedures and data collection.

The TTM-2 and TAME trials have been developed by teams of world-class investigators and extensive collaborations between the Australian and New Zealand Intensive Care Society Clinical Trials Group, the Australian Resuscitation Outcomes Consortium Centre of Research Excellence, the Medical Research Institute of New Zealand, the Swedish Research Council, the Swedish Heart–Lung Foundation, the Swedish national health system, the National Health and Medical Research Council of the Australian Government and the George Institute for Global Health. The teams have developed strong communication platforms and have worked hard to harmonise study elements such as enrolment criteria, data collection and management systems, ensuring that data collected by site research staff and blinded outcome assessors will be entered directly into a single, secure online electronic case report form once, but used by both trials for analysis. Randomisation will be undertaken by the study website, with stratification for co-enrolment and balanced allocation to ensure equal numbers of patients from each trial in the other. Talk has also turned to developing a single consent form to cover both trials where possible.

Multijurisdictional funding applications have been submitted to ensure that the studies are adequately

funded and will succeed. Securing funding from different jurisdictions is now a pivotal concept in global trials, with funding secured in one country encouraging funders in other countries and enhancing the success of the project.

An additional benefit of permissive co-enrolment into these two studies is that it ensures that an unconscious patient has access to both trials, rather than the site investigator determining which study the patient is enrolled in, and perhaps enrolling the patient in the one they consider "more suitable" for them. This removes charges of selection bias, while promoting patient autonomy (one of the basic principles of ethics in research involving human participants). Myles and colleagues suggest that allowing co-enrolment can enable research to be done more efficiently, thereby ensuring the just allocation of finances and availability of other resources to investigators to conduct research.[13] Although co-enrolment is not new, and is encouraged by many leading research groups, comprehensive study harmonisation is new and, crucially, will also reduce time spent collecting data and significantly reduce the time commitment from patients for follow-up.

One area of concern when harmonising two trials to this extent may be that, by enrolling patients into two or more trials, the scientific validity of the individual trials may be threatened.[13] Statistical data analysed in preparation for the harmonisation of TAME and TTM-2 showed no interaction between temperature control and $Paco_2$ in major outcomes in > 25 000 cardiac arrest survivors admitted to ICUs in Australia and New Zealand (Professor Rinaldo Bellomo, Faculty of Medicine, University of Melbourne, personal communication, 2017).

In conclusion, we suggest that the opportunity to comprehensively harmonise these two studies in this challenging patient population presents an exciting prospect and should become the benchmark for global trials in the future. This requires a high level of cooperation, trust and respect between study steering committees, investigators, funders and sites, which will bring about a revolution in how clinical trials are conducted in the ICU.

Competing interests

None declared.

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