Randomised controlled trials: the long hard climb to the summit — is there another way in the 21st century?

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Despite the rise of evidence-based medicine in the late 20th century,[1,2] clinicians must recognise that many aspects of day-to-day clinical practice, from optimal antibiotic dosing, fluid resuscitation and nutritional supplementation to sedation and ulcer prophylaxis, have an element of uncertainty or are open to challenge due to a lack of solid comparative data. As articulated in the minimum standards for level II and level III intensive care units by the College of Intensive Care Medicine in Australia and New Zealand, there is a need for major hospitals to embrace and support research as a component of care, including staffing by a full-time ICU research coordinator.[3] The potential benefits of ICU involvement in clinical research are significant. ICUs that undertake research create a climate of self-analysis, and patients enrolled into clinical trials may benefit by receiving greater attention and scrutiny of care.[4]

Well designed clinical trials, particularly Phase III and Phase IV trials, represent the pinnacle of evidence for evaluating new and existing therapies in critical care,[5] although not always in isolation from other trials and sources of evidence.[6] The would-be coordinating investigator, research coordinator and study management committee face a series of challenges that require careful preparation and planning, analogous to scaling a mountain. Our recent experience with a stepwise program of research[7,8] leads us to reflect on challenges in the conduct of clinical trials and to consider the future of ICU-based research into therapeutic interventions.[9-11]

Timelines are critical to success. The lead time for conducting a clinical trial is typically measurable in years. Demonstrated study feasibility, evidence to support likely treatment and outcome separation and an informed sample size are required to attract funding, often necessitating the need for pilot results.[5] Scientific rigour mandates that a clinical trial must have sufficient power to meet study objectives. In most cases this requires multicentre collaboration to achieve sufficient participant numbers, typically numbered in the hundreds for a Phase II trial[8,12,13] and in the thousands for a Phase III or Phase IV trial.[14-17] Advance publication of the statistical analysis plan is an important step to reduce bias.[8,18-23] Although regulatory and governance requirements are in place for valid reasons, they represent a daunting series of steps for project managers.[24] This approval phase is typically characterised by a series of delays as documents pass back and forth between sponsor, site, legal and research governance personnel before finalisation. The result is staggered site recruitment and longer recruitment times. After the study starts, a new series of challenges emerge, including maintaining adequate recruitment, addressing emergent issues, data monitoring and ensuring that reporting obligations are met. Our reflections on lessons learned in clinical trial project management are summarised in Table 1.

What does the future hold for clinical trials in critical care? It is safe to say that clinical trials will remain an integral part of the evaluation of new and existing therapeutic interventions. However, we believe increasingly varied combinations of collaborations will continue to emerge to address logistical issues associated with conducting such trials, including global networks variably comprising hospitals, research organisations, academia and the commercial sector. The role of observational data will become increasingly important as larger and more robust registries are better able to control for potential confounding variables and deliver generalisable evidence. The result may be increasingly powerful multicentre observational studies that reduce the lead time for clinical trials, as hypotheses are more effectively supported or rejected using existing data sources. Newer and novel study designs, such as pragmatic and registry-based randomised trials and cluster randomised trials, may similarly significantly reduce per-patient time associated with study-specific procedures.[25] The first of such trials in Australia and New Zealand is being planned. Opt-out consent, minimising data collection through use of existing data repositories, and reducing variation from standard practice by block randomisation may successfully hybridise research with pragmatic clinical care. Adaptive study designs may similarly improve flexibility and efficiency, although not without significant practical and statistical considerations.[26] Improved technology and access to user-friendly electronic case report forms will continue to have an important role to play, while the use of smartphones, tablet devices and direct communication between clinical and research databases holds further promise for efficient data capture. The trend towards a single ethics review pathway may reduce some delays,[24] but it is unlikely that many elements of the logistical, regulatory and governance landscape will change dramatically. Conducting clinical trials is still a long, at times rewarding and sometimes frustrating, climb to the summit.

Table 1. Logistical challenges in conducting investigator-initiated clinical trials

Challenge	Recommendations
Limited and highly competitive funding opportunities	Collaborate with experienced partners. Ensure funding applications address all aspects (scientific rigour, pilot and feasibility study results, track record). Consider multiple funding sources, including philanthropic, government and industry. Plan for top-up funding early on, if required, and consider consequences if successful or unsuccessful.
Ethics approval delays	Allow enough time for study planning and NEAF preparation; ensure protocol and study documents have gone through peer review before HREC submission. Be strategic with selection of the lead site for HREC submission; lead sites should have experience and adequate research coordinator time; use HRECs where there is an established relationship and familiarity with the submission process.
Multiple agreements (eg, clinical trial, drug supply, subcontractor agreements) across multiple jurisdictions	Experienced legal and contract support from the outset is mandatory; don't operate outside your level of experience, and ensure you follow organisational procedure for negotiating agreements. Speak directly to the decisionmaker when possible; don't rely on email communication. Use existing contracts that expedite site negotiation and approval.
Budget and financial management	A good business manager is vital to ensure incoming funds and outgoing payments are well managed; review the study budget regularly. Ensure the study budget is as accurate and realistic as possible, with relevant overheads and on-costs built in.
Burden of data collection	Limit number of required data fields by careful planning and pilot testing. Invest in a user-friendly electronic CRF database that is GCP-compliant; spend time developing logic and range checks for study variables to minimise errors (eg, autoqueries). Ensure there is sufficient research staffing at each site in your feasibility assessment.
Drug compounding and supply	Consider pharmaceutical industry support. Provide training materials and videos where sites are involved in drug compounding.
Variable research experience at study sites	Ensure the project management team is able to tailor support to the needs of the study site. Ensure study initiation covers relevant logistical aspects, including GCP. Establish a clear pathway for communication with the project management team, including after-hours support where needed.
Recruitment delays	Be realistic with recruitment targets, including conservative (worst-case) projections over the life of the study. Establish a mechanism to enable the project management team to be informed of study recruitment in real time. Monitor recruitment rates on a regular basis, comparing predicted and actual recruitment; revise predictions when there is reason to do so. Communicate with study sites often and consider recognition or incentives for milestone attainment. Identify and foster study champions.
Incomplete data	Ensure a planned monitoring approach. Regularly review CRF data during the life of the study. Establish data entry requirements from the beginning. Ensure there is a paper CRF that mirrors the electronic CRF. Develop supporting documents (eg, CRF guidelines and FAQs).
Serious adverse events	Accept that SAEs are part of a robust trial and need to be dealt with in a timely manner. Reinforce reporting requirements via training, CRF prompts, study materials and early site-monitoring visits.
Data monitoring committee	Establish clear expectations through a charter.
Data analysis	Develop a statistical analysis plan early on and make it available.
Authorship	Be clear about authorship early on.
Amendments to the protocol	Limit revisions of the protocol to those which are necessary for clarity or success of the study. Have a strong working relationship with the HREC. Have a sound knowledge of GCP requirements. Maintain excellence in record keeping.
Project management team	Ensure you have regular project management team and study management committee meetings. Celebrate successes. Provide regular communication to sites via newsletters, conferences and other appropriate means.
Study completion	Keep everyone motivated. Use strengths and recognise weaknesses of the study management team for completion.

NEAF = national ethics application form. HREC = human research ethics committee. CRF = case report form. GCP = good clinical practice. FAQs = frequently asked questions. SAEs = serious adverse events.

Competing interests

None declared.

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References

1 Evidence-Based Medicine Working Group. Evidence-based medicine. A new approach to teaching the practice of medicine. *JAMA* 1992; 268: 2420-5.

2 Cook DJ, Jaeschke R, Guyatt GH. Critical appraisal of therapeutic interventions in the intensive care unit: human monoclonal antibody treatment in sepsis. Journal Club of the Hamilton Regional Critical Care Group. *J Intensive Care Med* 1992; 7: 275-82.

3 College of Intensive Care Medicine of Australia and New Zealand. IC-01 Minimum Standards for Intensive Care Units. http://www.cicm.org.au/cms_files/IC-01%20Minimum%20Standards%20For%20Intensive%20Care%20Units%20-%20Current%20September%202011.pdf (accessed Mar 2014).

4 Majumdar SR, Roe MT, Peterson ED, et al. Better outcomes for patients treated at hospitals that participate in clinical trials. *Arch Intern Med* 2008; 168: 657-62.

5 McAuley DF, O'Kane C, Griffiths MJ. A stepwise approach to justify phase III randomized clinical trials and enhance the likelihood of a positive result. *Crit Care Med* 2010; 38 (10 Suppl): S523-7.

6 Ferreira ML, Herbert RD, Crowther MJ, et al. When is a further clinical trial justified? *BMJ* 2012; 345: e5913.

7 Dulhunty JM, Roberts JA, Davis JS, et al. Continuous infusion of beta-lactam antibiotics in severe sepsis: a multicenter double-blind, randomized controlled trial. *Clin Infect Dis* 2013; 56: 236-44.

8 Dulhunty JM, Roberts JA, Davis JS, et al. A protocol for a multicentre randomised controlled trial of continuous beta-lactam infusion compared with intermittent beta-lactam dosing in critically ill patients with severe sepsis: the BLING II study. *Crit Care Resusc* 2013; 15: 179-85.

9 Australian Government Department of Health and Ageing. Strategic review of health and medical research. Better health through research. Final report, February 2013. http://www.mckeonreview.org.au/downloads/Strategic_Review_of_Health_and_Medical_Research_Feb_2013-Final_Report.pdf (accessed Mar 2014).

10 House of Commons Science and Technology Committee. Clinical trials: third report of session 2013-14. HC104. London: The Stationery Office, 2013. http://www.publications.parliament.uk/pa/cm201314/cmselect/cmsctech/104/104.pdf (accessed Mar 2014).

11 Institute of Medicine (US) Forum on Drug Discovery, Development, and Translation. Transforming clinical research in the United States: challenges and opportunities. Workshop summary. Washington, DC: National Academies Press, 2010. http://www.ncbi.nlm.nih.gov/books/NBK50892 (accessed Mar 2014).

12 Parke R, McGuinness S, Dixon R, Jull A. Open-label, phase II study of routine high-flow nasal oxygen therapy in cardiac surgical patients. *Br J Anaesth* 2013; 111: 925-31.

13 Kruger P, Bailey M, Bellomo R, et al. A multicenter randomized trial of atorvastatin therapy in intensive care patients with severe sepsis. *Am J Respir Crit Care Med* 2013; 187: 743-50.

14 Wunderink RG, Laterre PF, Fancois B, et al. Recombinant tissue factor pathway inhibitor in severe community-acquired pneumonia: a randomized trial. *Am J Respir Crit Care Med* 2011; 183: 1561-8.

15 Ranieri VM, Thompson BT, Barie PS, et al. Drotrecogin alfa (activated) in adults with septic shock. *N Engl J Med* 2012; 366: 2055-64.

16 Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med* 2012; 367: 1901-11.

17 NICE-SUGAR Study Investigators, Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009; 360: 1283-97.

18 Finfer S, Bellomo R. Why publish statistical analysis plans? *Crit Care Resusc* 2009; 11: 5-6.

19 Young PJ, Weatherall M, Saxena MK, et al. Statistical analysis plan for the HEAT trial: a multicentre randomised placebo-controlled trial of intravenous paracetamol in intensive care unit patients with fever and infection. *Crit Care Resusc* 2013; 15: 279-86.

20 Pike F, Yealy DM, Kellum JA, et al. Protocolized Care for Early Septic Shock (ProCESS) statistical analysis plan. *Crit Care Resusc* 2013; 15: 301-10.

21 Power GS, Harrison DA, Mouncey PR, et al. The Protocolised Management in Sepsis (ProMISe) trial statistical analysis plan. *Crit Care Resusc* 2013; 15: 311-7.

22 Delaney AP, Peake SL, Bellomo R, et al. The Australasian Resuscitation in Sepsis Evaluation (ARISE) trial statistical analysis plan. *Crit Care Resusc* 2013; 15: 162-71.

23 Myburgh J, Li Q, Heritier S, et al. Statistical analysis plan for the Crystalloid Versus Hydroxyethyl Starch Trial (CHEST). *Crit Care Resusc* 2012; 14: 44-52.

24 Hicks SC, James RE, Wong N, et al; Australasian Gastro-Intestinal Trials Group. A case study evaluation of ethics review systems for multicentre clinical trials. *Med J Aust* 2009; 191: 280-2.

25 Lauer MS, D'Agostino RB Sr. The randomized registry trial – the next disruptive technology in clinical research? *N Engl J Med* 2013; 369: 1579-81.

26 Chow SC. Adaptive clinical trial design. *Annu Rev Med* 2014; 65: 405-15. ❑