



Online Appendix

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Online Appendices

Supplement to:

The cost-effectiveness of early goal directed therapy: an economic evaluation alongside the
ARISE trial

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APPENDIX 1

1. ARISE Investigators

The ARISE Study is a collaboration of the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG), The Australasian College for Emergency Medicine and the Australian and New Zealand Intensive Care Research Centre (ANZIC-RC), Monash University. The writing committee vouches for the accuracy and completeness of the data, the statistical analysis and the fidelity of the final report to the study protocol.

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APPENDIX 2

2. eMethods

2.1 Measures of effectiveness

Survival:

Trial-based outcomes such as hospital and 90-day survival were extracted directly from the data collection for the ARISE RCT for the entire trial population. Survival status to one-year was determined using medical records, or contact with the participant, their next of kin, or general practitioner. Where a participant was deceased, the date of death was recorded. In patients who were randomised prior to ethics approval for long-term follow-up or in participants who had declined consent to be contacted for QOL assessments, and where ethics approval was granted, hospital records were searched to determine participants' survival status at 1-year post randomisation. In addition, where patients were not able to be located or contacted to complete QOL assessments, hospital records were searched to determine survival status.

Quality of life:

Quality of life assessments occurred at baseline, 6 and 12 months post randomisation in all patients participating in the ARISE RCT and randomised after ethics approval was granted for long-term follow up. At each time point, three QOL questionnaires were completed - the EuroQoL EQ5D-3L, the Medical Outcomes Study Short Form 36 version 2 (SF-36), and the Assessment of Quality of Life (AQoL) instrument. These generic measures were chosen as there are no critical-care specific or sepsis specific quality of life outcome measures. The EQ5D-3L was used to determine utilities for use in QALY calculations.

For participants recruited in Australia and New Zealand, site research staff sent a QOL referral form to the trial-coordinating centre after the 90-day survival assessment had been completed. Just prior to 6 months following randomisation, the trial co-coordinating centre mailed a cover letter, the QOL questionnaires and a stamped, addressed envelope (to return the completed questionnaires) to all participants known to be alive following their 90-day assessment. Where participants did not return the questionnaires, follow-up contact via telephone was conducted by a central, blinded assessor with participants instructed to return the completed questionnaires and given the option to provide answers to the EQ-5D-3L over the phone. These phone calls were made at various times and on both weekdays and weekends to maximise the chances of contacting the patient. Similar methods were used just prior to 12 months following randomisation, in participants known to be alive at the prior assessment point.

2.2 Assessment of resource use

The case report form (CRF) for the ARISE RCT collected data on all patients for the following ED and in-hospital resources:

ED:

- Duration of ED stay
- Type and volume of IV fluid received

- Type and volume of blood products received
- Type and dose of vasoactive drugs received

Hospital:

- Duration of ICU stay
- Duration of hospital stay
- Insertion of invasive monitoring (e.g. arterial line, ScvO₂ catheter) to 72 hours post randomisation (including in the ED)
- Type and volume of IV fluid received to 72 hours post randomisation
- Type and volume of blood products received to 72 hours randomisation
- Type and dose of vasoactive drugs received to 72 hours randomisation
- Antimicrobial therapy received
- Surgery from ED presentation to 72 hours post randomisation
- Use of corticosteroids from ED presentation to 72 hours post randomisation
- Use of and duration of invasive mechanical ventilation
- Use of and duration of non-invasive mechanical ventilation
- Use of and duration of vasopressor drug support
- Use of and duration of renal replacement therapy
- Acute hospital readmission to 90 days post randomisation

Additional detailed resource use was collected the 205 patients in the health economic evaluation substudy usual care and EGDT patients through completion of a detailed case report form (CRF) which was developed for the sub-study. The CRF collected data on the following:

- Australian refined diagnosis related group (AR-DRG)
- Principal diagnosis ICD-10 AM code
- Daily allied health consultations
- Daily pathology testing – type and number of tests
- Daily diagnostic radiology – type and number of tests
- Daily type and volume of IV fluid received
- Daily type and volume of blood products received
- Daily type and volume of nutrition (EN or TPN) received
- Daily medications received
- Daily organ supports and procedures (such as ECGs)
- Daily line and catheter insertion and/or removal
- Details of all surgeries performed (including procedure code)

- Details of renal replacement therapy and consumables used
- Details of ECMO therapy and consumables used
- Readmission to acute hospitals up to 12 months following randomisation including LOS, ICU admission, AR-DRG for the admission and text description for the reason for admission
- Admission to rehabilitation facilities and length of stay
- Admission to long term care facilities and length of stay

This CRF was completed by study research coordinators at each site participating in the ARISE RCT economic evaluation substudy.

For the EGDT group, specific resources attributable to implementation of EGDT were collected by determining the equipment used in the delivery of the protocol (for example, central venous catheter capable of ScvO₂ monitoring, the use of catheter insertion-related consumables, and IV fluids, medications and blood products used in delivering the protocol), estimating the additional staff time required for implementation of the protocol (for example, medical and nursing staff time for insertion of an ScvO₂ catheter and additional monitoring time during the 6 hour protocol), as well as an estimate of resources required per site for training and ongoing monitoring. The level of additional staff time required to deliver EGDT was estimated according to expert opinion. In determining the resources per patient associated with the use of the monitor, it was assumed each site required 2 monitors and each monitor had a 5-year life cycle.

Estimates of additional healthcare resource use beyond hospital discharge were collected at six and twelve months post randomisation through the use of a patient diary. This diary was provided to patients by the site research coordinator (at sites participating in the ARISE RCT economic evaluation substudy) prior to discharge. When participating patients were sent their 6 months QOL forms, they were instructed to return their completed diary (for 0 to 6 months) with their QOL forms. A patient diary for collection of additional healthcare resource use between 6 and 12 months following randomisation was mailed to participating patients with their 6 month QOL forms with instructions about completing the diary in the cover letter. Where participants did not return the diary, follow-up contact via telephone was conducted by a central, blinded assessor who requested data about healthcare use since discharge (or from 6 to 12 months at the final follow up) and recorded this in a diary.

The patient diary collected data on the following:

- Number of specialist medical appointments
- Number of GP appointments
- Number of allied health or other (e.g. nursing) consultations
- Acute hospital readmissions - length of stay and reason for admission
- Rehabilitation admissions - length of stay
- Long term care facility admissions – type and length of stay

Patient-reported readmissions to hospital were compared with site data on readmissions with site data used in preference to patient data where there was a discrepancy and the readmission occurred at the site collecting the data.

2.3 Calculation of costs

Items of health care resource utilisation were combined with relevant unit costs to develop total costs for individual patients for each treatment group. Multivariate regression analysis was used to identify patient and hospital level characteristics associated with increased costs of care.

2.3.1 Staffing costs

Emergency department staffing costs

Medical staffing costs in the ED were determined using the Independent Hospital Pricing Authority (IHPA) Emergency care clinician time consensus study - report of final results.¹ This report provided estimates of time taken for common activities conducted with the ED (determined by clinicians through a Delphi consultation process). To determine the time associated with various standard ED activities, it was assumed that all patients in the ARISE study were within the “complex case-illness” classification.

eTable 8 shows the time and costs associated with standard ED medical tasks. In the IHPA report, times were for consultant medical staff performing the activities, with estimated procedure time increased for medical staff with less experience by the following percentages: registrar 20%, resident 50%. For this economic evaluation, it was assumed that all initial medical ED activities in eTable 8 were performed by a registrar (unless otherwise specified).

In determining the nursing staff costs in the ED, it was assumed that patients enrolled in the ARISE RCT were sufficiently ill to require a 1:2 nursing ratio, with 50% of ED time required for assessment, monitoring, review and other standard activities. Additional time and costs required to implement the EGDT intervention are reported separately. Costs for additional time (for both medical and nursing staff) required for insertion of lines or catheters or for other procedures (such as ventilator set-up) were included within the cost of the procedures.

The total costs for ED staffing were calculated by multiplying the total time taken (in hours) by the appropriate staff member hourly rate. The hourly rate for nursing and medical staff was determined using the average of 2014 (where available) enterprise agreement salaries in WA, NSW, Victoria and SA.²⁻⁹ An additional 20% was added to each hourly wage to incorporate routine on-costs. On-costs represent costs in addition to salaries and wages; such as payroll tax, superannuation, workers' compensation and other liability insurance, and leave loading. The hourly wages for each type of staff member is presented in eTable 9.

Intensive Care Unit staffing costs

Staffing costs in the ICU were determined using data from the ANZICS Critical Care Resources (CCR) registry. The CCR registry collects data related to the provision and utilisation of critical care resources in Australia and New Zealand. Staff from ANZICS provided the raw survey data, including data on the major components of expenditure (cost blocks), from the 2103/2014 survey for Australian sites who participated in the ARISE RCT.

From this data, the daily ICU staffing costs were determined by summing the total yearly expenditure on staffing (medical, nursing, and non-clinical staff) at each site and dividing this by the number of bed-days in the same year. The average daily cost was then calculated as the average of the daily ICU staffing costs at each site (participating in both the CCR survey and the ARISE RCT). As the CCR survey explicitly excludes overhead costs, an additional 20% was added to the daily ICU staffing costs to allow for organisational overhead costs. The daily ICU staffing costs are presented in eTable 10.

Ward staffing costs

Staffing costs in the ward were determined using the average daily ward cost from 2017/2018 (converted to 2014 AUD) from all wards at the Alfred Hospital, Melbourne, excluding elective admission units and short stay units. These daily costs include both staffing costs and consumables, along with overhead costs. The daily ward staffing costs are presented in eTable 10.

Allied health and other consultation costs

The number and type of allied health and other consultations (e.g. specialist nursing consultation such as a stomal nurse) were recorded daily. Each consultation was costed using award rates,^{5,10,11} with 20% added to account for on-costs. The rates for each inpatient allied health or other consultation are shown in eTable 10.

2.3.2 Procedure costs

The type and number of procedures occurring were recorded daily. Procedure costs included costs for surgeries, catheter or line insertions, and other procedures such as haemodialysis, ventilation, non-invasive ventilation and ECMO. Surgeries were costed using the 2014 MBS schedule fee with the addition of assistant fees and anaesthetic fees based on the surgical time, as described in the MBS schedule.¹²

Catheter and line insertion costs included costs of consumables required for the insertion, capital costs for bedside ultrasound where required, and staffing costs. Times taken by medical and nursing staff to perform insertions of catheters and lines were taken from the IHPA Emergency care clinician time consensus study report of final results.¹ Where times for specific catheters or lines were not available in the IHPA report, the time used was the average of times reported by a convenience sample of critically care trained medical and nursing staff. Staffing costs were determined using the time taken and the hourly staff wages as shown in eTable 9. Staffing costs for catheter and line insertions were only included when the catheter or line was inserted in the ED as the staffing costs in both ICU and the ward are captured using a daily cost as described above. Costs for consumables (including catheters and lines) were obtained from participating sites where available and the average of provided costs used. The cost associated with each catheter or line insertion is shown in eTable 11.

Costs for ventilation or non-invasive ventilation set-up were collected similarly to those for catheter and line insertions, with staff times taken from the IHPA report,¹ or the average of times reported by a convenience sample of critically care trained medical and nursing staff. Staff costs were only included where procedures occurred in the ED. Costs for continuous haemodialysis were calculated using staffing time for set-up (as described for ventilation) and

the cost of consumables, including catheters, circuits, dialysate and replacement fluids, and regional anti-coagulation. Ongoing continuous haemodialysis daily costs included catheters or circuit changes, daily volumes of dialysate and replacement fluids, and regional anti-coagulation. Costs for intermittent haemodialysis were calculated using the National Hospital Cost Data Collection (NHCDC) Haemodialysis - hospital based Tier 2 cost for 2013/2014.¹³ Costs for ECMO were similar to continuous haemodialysis with costs for catheter and circuit changes included daily. Costs for procedures performed by staff external to ED, ICU and the wards were determined using the MBS schedule fee for the specific procedure (e.g. EEG). Costs associated with ventilation, non-invasive ventilation, haemodialysis, ECMO and other procedures are detailed in eTable 11.

Procedures performed in radiology, such as insertion of a Hickman line or Permacath, were included in imaging costs as described below.

2.3.3 Pathology and imaging costs

The number and type of pathology and imaging tests received by each patient were recorded daily. Costs for each individual pathology or imaging tests were determined using the average cost for each test obtained from participating sites where available. Where costs were not available from sites for specific tests, MBS schedule fees were used.

2.3.4 Medication costs

Details of medications received while patients remained in hospital were recorded daily. Other than for vasoactive medications, doses of each medication were not collected, due to the data burden. Average daily doses of each medication for a patient meeting ARISE RCT criteria were determined via the expert opinion of an experienced ICU pharmacist and/or ICU consultant. Where medications were given by IV infusion, the cost of any fluid for dilution (for example, 5% dextrose or 0.9% Normal saline) and the cost of the IV line were added to medication cost. Where medications required a low sorbing intravenous line, this cost was added in lieu of the cost of a standard IV line. Costs for each individual medication dose was determined using 2014 medication costs provided by the Austin hospital. Where costs were not available for specific medications, the dispensed price for maximum quantity (DPMQ) from the Pharmaceutical Benefits Scheme was used, adjusted to the required dose.¹⁴

The type and dose of vasoactive medications used was collected in the ARISE RCT CRF. Doses were collected at 24 and 72 hours post randomisation. It was assumed that the dose received at 24 hours post randomisation was the dose received at any time up until day 2. The dose received at 72 hours post randomisation was the dose received at any time from day 2 while the vasoactive agent was being received. Costs of vasoactive agents were provided by the Austin hospital and adjusted to the dose received by the patient.

2.3.5 Fluid costs

The type and volume of intravenous fluids (other than those specific for medication delivery), blood products and intravenous or enteral nutrition were recorded daily. Costs of the intravenous fluids, other than albumin and hydroxyethyl starch, were determined using the average cost for each fluid type obtained from participating sites where available, adjusted for

the volume received. The costs of different blood products received (including albumin) were determined using the prices published by the National Blood Authority (NBA) for fresh blood components or plasma and recombinant blood products supplied under contract in 2013-14.¹⁵ Costs were adjusted based on the number of units or volume of each type of blood product received. The costs of total parenteral nutrition (TPN) and enteral nutrition (EN) were obtained directly from the companies who supplied these products to sites in 2014. Costs were adjusted based on the volume of nutrition received daily.

2.3.6 Additional EGDT costs

Implementation of the EGDT intervention required additional equipment, staff time and training. The additional costs of the PreSep™ ScvO₂ catheter and the associated Vigileo monitor were included for patients randomised to EGDT. In addition, based on expert opinion, it was assumed that each hour of EDGT required an additional 10 minutes of nursing time compared to usual care.¹⁶ To provide EGDT as part of routine practice required additional formal or informal training beyond the existing hospital education program. It was assumed that at each site each clinical member of ED staff required 30 minutes of additional training to be competent to deliver EGDT. The total training time for introducing the EGDT protocol into the ED was then calculated for each site in the trial. Based on the Australasian College of Emergency Medicine (ACEM) data, the average mix of ED staff was assumed to be eight consultants, 12 registrars, 19 junior doctors and 65 nurses.¹⁷ It was assumed that medical consultants required training every five years, registrars and nurses every two years and residents every year. The total additional costs associated with EGDT are shown in eTable 12.

2.3.7 Capital equipment costs

Where appropriate, the costs of capital equipment were included in the total patient costings. Capital expenditure was included for bedside ultrasound (to assist with line insertions such as ScvO₂ and CVCs), ventilators, non-invasive ventilators, ECMO machines, haemodialysis machines, IV pumps, ICU beds and chairs and bedside resuscitation equipment. For each item of capital expenditure, costs were allocated on a per patient or per procedure level (as appropriate), according to the life span of the equipment, the expected usage (based on number of eligible patient or proportion of time in use), assuming 5% interest fully depreciated over the lifespan of the equipment. Capital equipment prices were sourced directly from the manufacturers, or from sites where unavailable from the manufacturers. Capital equipment costs did not include annual maintenance costs or sterilisation costs. Capital expenditure for ward equipment was not included. Details of capital expenditure costs per patient (or per procedure or per bed day as appropriate) are shown in eTable 13.

2.3.8 Additional inpatient costs

The data on ED costs includes medical and nursing staffing time, consumables, pathology, imaging and medications as outlined above. It does not include costs for non-clinical staff, hotel, depreciation and other costs. The IHPA Emergency care costing and classification project reports that, in 2013/2014, medical and nursing staffing time, consumables, pathology, imaging and medications contributed 80.4% to total ED costs, with non-clinical staff and other

costs contributing 19.6%. To enable ED costs to more accurately reflect actual costs incurred, measured ED total costs were increased by 24% (19.6/80.4).

Additional costs for each ICU day were included to account for the cost of medical gases in ICU, using expenditure data. The cost (\$8.11 per ICU day) was calculated from the ANZICS CCR registry with the total yearly expenditure on medical gases at each site divided by the number of bed-days in the same year. The average daily cost was then calculated as the average of the daily ICU medical gases costs at each site (participating in both the CCR survey and the ARISE RCT). Costs for medical gases in ED and the ward were not included due to a lack of available data.

2.3.9 Post discharge costs

Site research staff collected data on readmission dates, rehabilitation and long term care and this was supplemented by data from a patient diary that was completed by patients post discharge to one year. Outpatient appointment costs (for example, medical and allied health appointment costs) were not available for patients who died following discharge but prior to a follow-up point (at either 6 or 12 months). While readmission, rehabilitation and long term care costs were available, total costs post discharge may be underestimated due to the exclusion of follow up outpatient appointment costs for these patients (n=10).

Costs for readmissions were based on the AR-DRG associated with the admission and obtained from the NHCDC Public Hospitals Round 18 cost report, which provides the average cost for an admission for a given AR-DRG in 2013/2014.¹³ The costs for rehabilitation and long term care were based on the length of stay with the daily costs obtained from NHCDC Round 18 cost report. Costs for outpatient appointments were primarily taken from the MBS Schedule, with additional sources as required. The unit costs associated with post-discharge healthcare resource use are shown in eTable 14.

Non-healthcare costs were not included in the cost-effectiveness analysis. The inclusion of non-healthcare costs is controversial with some researchers assuming that QALYs reflect the full effects on health status, including the burden of lost productivity costs, whilst others, including the United States Public Health Service Panel on Cost and Effectiveness in Health and Medicine (PCEHM), do not recommend including non-healthcare costs.¹⁸ As per the recommendations of the PCEHM, non-healthcare costs were not included in the primary analyses.

All costs were expressed as 2014 Australian dollars (AUD). Where the year of unit costs provided was not 2014, costs were converted to 2014 AUD using the Australian Bureau of Statistics (ABS) consumer price index for the medical and hospital services subgroup.¹⁹

2.4 Sensitivity analyses

Sensitivity analyses were conducted on a range of parameters reflecting our estimates and assumptions regarding costs of care, along with assumptions about the distribution of the data. Sensitivity analyses were conducted to assess the effect of various assumptions in the cost-effectiveness analyses. Given the impact of ongoing long term care (LTC) on overall costs, the sensitivity analysis explored different unit cost inputs for the daily cost of high level care,

assuming a resource utilisation group (activities of daily living) level of 4-10, rather than 11-18 in the primary analysis. This results in daily high level LTC costs of \$747.45 compared to \$845.31. The impact of costing acute care re-admissions based on length of stay rather than AR-DRG was also explored. The average cost of an acute care bed day (\$1,839 based on NHCDC Round 18¹³) was used to determine a total readmission cost based on total readmission days.

The primary analysis was based on unadjusted costs and outcomes without any adjustments for covariates, assuming randomisation ensured no imbalance in key predictors of cost. In the sensitivity analysis, costs were adjusted for the same predefined baseline covariates as in the primary ARISE RCT analysis - age, APACHE II score, systolic blood pressure (< 90 mm Hg or \geq 90 mm Hg), and presence/absence of mechanical ventilation (excluding country as the economic evaluation focuses on Australia). Additional baseline covariates identified as significant predictors of cost in the regression model, described above, were also included.

In additional sensitivity analyses, alternative distributional assumptions about costs and QALYs were assessed to determine the robustness of the results. A generalised linear model was used, with distribution families selected using the Modified Park Test, and the link function using the Pearson Correlation, Pregibon Link and Modified Homer and Lemeshow tests. The model was run using the same baseline covariates described in the paragraph above.

The cost-effectiveness analyses used data from a sub-sample of patients in whom detailed costing data was available. As there were no significant differences between patients in whom costing was available and those without costing, an additional sensitivity analysis was performed determining the cost-utility of EGDT compared to usual care utilising all available QALY data (n=1387) alongside the cost data for the sub-sample.

APPENDIX 3

3. Supplementary Tables

eTable 1 Sites participating in the ARISE RCT economic evaluation substudy

| Participating sites | Hospital type^a | Number of hospital beds | ED presentations annually^b | Trial recruitment period | Total number of patients recruited | EGDT delivery location | Number of patients economic evaluation substudy |
|----------------------------------|----------------------------------|--------------------------------|--|---------------------------------|---|-------------------------------|--|
| Australia | | | | | | | |
| The Alfred Hospital | Tertiary, metro | 448 | 54528 | Jan 10 - Apr 14 | 45 | ICU or ED | 11 |
| Austin Health | Tertiary, metro | 980 | 68735 | Oct 08 - Apr 14 | 142 | ICU or ED | 23 |
| Blacktown Hospital | Non-tertiary, metro | 400 | 34200 | Aug 09 - Apr 14 | 46 | ICU | 7 |
| Canberra Hospital | Tertiary, metro | 672 | 60868 | June 09 - Apr 14 | 50 | ICU or ED | 13 |
| Central Gippsland Health Service | Non-tertiary, rural | 280 | 15226 | Oct 09 - Apr 14 | 25 | ICU | 6 |
| Geelong Hospital | Tertiary, metro | 406 | 56184 | Apr 11 - Apr 14 | 10 | ICU or ED | 5 |
| Hornsby Hospital | Non-tertiary, metro | 300 | 30705 | Aug 09 - Apr 14 | 42 | ICU or ED | 5 |
| Ipswich Hospital | Non-tertiary, metro | 304 | 47186 | Jun 11 - Apr 14 | 19 | ICU | 4 |
| Liverpool Hospital | Tertiary, metro | 855 | 61957 | Nov 08 - Apr 14 | 73 | ICU | 9 |
| Monash Medical Centre | Tertiary, metro | 640 | 68631 | Dec 10 - Apr 14 | 19 | ICU or ED | 3 |
| Nepean Hospital | Tertiary, metro | 520 | 52202 | Jul 09 - Apr 14 | 38 | ED | 5 |
| Royal North Shore Hospital | Tertiary, metro | 740 | 58401 | Oct 08 - Apr 14 | 150 | ICU or ED | 31 |
| Royal Perth Hospital | Tertiary, metro | 833 | 67441 | Nov 08 - Apr 14 | 51 | ICU or ED | 7 |
| Royal Prince Alfred Hospital | Tertiary, metro | 970 | 62199 | Oct 10 - Apr 14 | 111 | ICU or ED | 27 |
| St. Vincent's Hospital, Sydney | Tertiary, metro | 350 | 41511 | Jul 09 - Apr 14 | 30 | ICU or ED | 4 |
| Sydney Adventist Hospital | Non-tertiary, metro | 360 | 20000 | Jul 12 - Apr 14 | 27 | ICU or ED | 12 |

| Participating sites | Hospital type^a | Number of hospital beds | ED presentations annually^b | Trial recruitment period | Total number of patients recruited | EGDT delivery location | Number of patients economic evaluation substudy |
|------------------------------|----------------------------------|--------------------------------|--|---------------------------------|---|-------------------------------|--|
| The Queen Elizabeth Hospital | Tertiary, metro | 311 | 41539 | Oct 08 - Apr 14 | 118 | ICU | 14 |
| New Zealand | | | | | | | |
| Christchurch Hospital | Tertiary, metro | 650 | 65000 | Oct 09 - Apr 14 | 45 | ICU | 11 |
| Middlemore Hospital | Tertiary, metro | 800 | 90000 | Nov 09 - Apr 14 | 43 | ICU or ED | 6 |

ED=emergency department; EGDT=early goal directed therapy; ICU=intensive care unit

^a Classification of Australian and New Zealand participating sites as tertiary (academic) and non-tertiary and metropolitan and rural according to the Australian and New Zealand Intensive Care Society Centre for Outcomes Research. Classification of other sites self-reported.

^b Based on the number of ED presentations between July 2010 and June 2011.

eTable 2 Baseline characteristics of the patients participating in the economic evaluation sub-study compared to those not participating

| Baseline characteristic | Costed trial participants (n = 203) | Non-costed trial participants (n = 1,387) | p-value |
|--|--|--|----------------|
| Male gender, n (%) | 116 (57.1) | 834 (60.1) | 0.44 |
| Age, yr, mean (SD) | 63.34 (16.80) | 62.84 (16.43) | 0.69 |
| Acute Physiology and Chronic Health Evaluation II score, mean (SD) | 15.84 (7.05) | 15.55 (6.44) | 0.55 |
| Mechanical ventilation, n (%) | 12 (5.9) | 122 (8.8) | 0.22 |
| Vasopressor infusion, n (%) | 32 (15.8) | 223 (16.1) | 1.00 |
| Charlson comorbidity score (1 or more), n (%) | 118 (58.1) | 785 (56.6) | 0.71 |
| Usual accommodation, n (%) | | | |
| Home | 194 (95.6) | 1313 (94.7) | 0.74 |
| Long-term facility | 9 (4.4) | 74 (5.3) | |
| Mortality n/N (%) | | | |
| Hospital | 38/203 (18.7) | 205/1386 (14.8) | 0.15 |
| 12 months | 63/203 (31.0) | 348/1311 (26.5) | 0.20 |

SD=standard deviation

eTable 3 Additional post-discharge resource use

| Post discharge resource use | EGDT (n=98) | Usual care (n=105) |
|---|--------------------|---------------------------|
| Readmissions | | |
| Number of overnight readmissions, mean (SD) | 1.3 (1.8) | 0.8 (1.3) |
| Number of ED or day admission, mean (SD) | 1.6 (7.5) | 1.9 (15.0) |
| Total number of readmission, mean (SD) | 3.0 (8.1) | 2.8 (15.2) |
| Long Term Care | | |
| High level long term care, n(%) | 8 (8.2%) | 5 (4.8%) |
| High level long term care LOS, mean ± SD | 16.1 (68.5) | 10.1 (54.7) |
| Low level long term care, n(%) | 2 (2.0%) | 1 (1.0%) |
| Low level long term care LOS, mean ± SD | 0.9 (6.5) | 0.1 (1.4) |
| Outpatient/community consultations | | |
| Medical - | | |
| GP, mean (SD) | 7.9 (9.9) | 6.4 (8.1) |
| Specialist, mean (SD) | 3.7 (5.6) | 4.2 (7.5) |
| Allied health | | |
| Physiotherapy, mean (SD) | 3.3 (15.4) | 1.8 (7.7) |
| Occupational therapy, mean (SD) | 0.4 (4.0) | 0.4 (3.4) |
| Dietitian, mean (SD) | 0.2 (0.8) | 0.2 (1.1) |
| Osteopath/Chiropractor, mean (SD) | 0.1 (0.9) | 0.6 (3.3) |
| Social worker, mean (SD) | 0.3 (2.6) | 0.1 (0.6) |
| Psychologist, mean (SD) | 0.2 (1.3) | 0.4 (3.5) |
| Speech therapist, mean (SD) | 0.0 (0.1) | 0.2 (2.2) |
| Other | 0.4 (1.7) | 0.4 (1.7) |
| Other | | |
| Carers | 3.4 (16.4) | 1.7 (17.8) |

ED=emergency department; EGDT=early goal directed therapy; LOS=length of stay; SD=standard deviation

eTable 4 Average per patient costs for various cost components

| | Average costs (2014 AUD), mean (SD) | |
|--------------------------|-------------------------------------|--------------------|
| | EGDT (n=98) | Usual care (n=105) |
| Procedures | | |
| Surgery | \$175 (\$428) | \$364 (\$877) |
| Line/catheter insert | \$1,083 (\$518) | \$609 (\$436) |
| Haemodialysis | \$180 (\$594) | \$313 (\$860) |
| Other procedures | \$183 (\$456) | \$120 (\$180) |
| Radiology | | |
| X-ray | \$295 (\$265) | \$289 (\$257) |
| CT | \$408 (\$575) | \$457 (\$533) |
| MRI | \$12.19 (\$121) | \$10.17 (\$59.88) |
| Ultrasound | \$141 (\$192) | \$161 (\$212) |
| Nuclear medicine | \$89.87 (\$341) | \$62.66 (\$255) |
| Fluoroscopy | \$3.49 (\$17.08) | \$4.76 (\$17.91) |
| CT angiography | \$37.01 (\$186) | \$70.80 (\$196) |
| Interventional radiology | \$53.24 (\$287) | \$63.08 (\$214) |
| Total fluids | | |
| IV fluids | \$113 (\$259) | \$125 (\$291) |
| Blood products | \$577 (\$1,629) | \$857 (\$1,814) |
| Nutrition | \$55.17 (\$216) | \$63.81 (\$283) |
| Medications | | |
| Antibiotics | \$217 (\$332) | \$233 (\$288) |
| Antivirals | \$33.24 (\$238) | \$13.25 (\$88.56) |
| Antifungals | \$299 (\$2,051) | \$358 (\$2,603) |
| Sedatives | \$155 (\$487) | \$111 (\$297) |
| Paralytics | \$2.14 (\$7.08) | \$1.18 (\$3.15) |
| VTE prophylaxis | \$47.57 (\$160) | \$27.31 (\$38.64) |
| Stress ulcer prophylaxis | \$11.45 (\$24.92) | \$11.35 (\$21.54) |
| Steroids | \$10.47 (\$19.99) | \$13.58 (\$25.73) |
| Vasopressor | \$147 (\$350) | \$115 (\$210) |
| Other medications | \$143 (\$648) | \$47.23 (\$74.09) |

EGDT=early goal directed therapy; AUD=Australian dollars; SD=standard deviation;
IV=intravenous; VTE=venous thromboembolism

eTable 5 Total inpatient costs by location

| Location | | EGDT (n=98) | Usual care (n=105) |
|----------|---------------------------|-------------------|--------------------|
| ED | LOS, hours, mean (SD) | 4.38 (1.81) | 5.00 (2.49) |
| | Costs 2014 AUD, mean (SD) | \$1,623 (832) | \$1,489 (720) |
| ICU | LOS, days, mean (SD) | 4.27 (4.06) | 4.51 (4.71) |
| | Costs 2014 AUD, mean (SD) | \$23,456 (21,041) | \$23,051 (22,314) |
| Ward | LOS, days, mean (SD) | 10.24 (22.20) | 9.29 (11.15) |
| | Costs 2014 AUD, mean (SD) | \$5,446 (5,819) | \$5,910 (6,196) |

ED=emergency department; EGDT=early goal directed therapy; LOS=length of stay; SD=standard deviation; AUD=Australian dollars

eTable 6 Cost effectiveness at one year: subgroup analyses

| Subgroup | Incremental costs, mean (95% CI) (2014 AUD) | Incremental QALYs, mean (95% CI) | ICER (cost/QALY) |
|----------------------------------|---|----------------------------------|------------------|
| Gender | | | |
| Male | \$12,623 (-\$12,554-\$37,801) | -0.054 (-0.164-0.057) | Dominated |
| Female | \$13,549 (-\$13,822-\$40,921) | -0.035 (-0.153-0.084) | Dominated |
| Age (years) | | | |
| ≤65 | \$1,503 (-\$19,276 -\$22,282) | -0.139 (-0.253 to -0.024) | Dominated |
| >65 | \$25,727 (-\$5,052-\$55,507) | 0.025 (-0.086-0.135) | \$1,043,764/QALY |
| APACHE II score | | | |
| ≤24 | \$12,831 (-\$6,927-\$32,589) | -0.048 (-0.131-0.035) | Dominated |
| >24 | \$13,363 (-\$34,288-\$61,013) | -0.157 (-0.352-0.037) | Dominated |
| Presentation type | | | |
| Hypotension only | \$27,143 (-\$424-\$54,710) | -0.064 (-0.163-0.036) | Dominated |
| Hyperlactataemia only | \$6,437 (-\$11,136-\$24,009) | -0.024 (-0.190-0.143) | Dominated |
| Hypotension and hyperlactataemia | -\$15,849 (-\$65,130-\$33,432) | -0.057 (-0.275-0.161) | \$277,417/QALY |

CI=confidence interval; AUD=Australian dollars; QALYs= quality-adjusted life years; ICER=incremental cost-effectiveness ratio

eTable 7 Cost effectiveness at one year: sensitivity analyses

| Sensitivity analysis | Incremental costs, mean (95% CI) (2014 AUD) | Incremental QALYs, mean (95% CI) | ICER (cost/QALY, 95% CI¹) |
|---|--|---|---|
| Altering high level LTC costs | \$12,455 (-\$5,053-\$29,963) | -0.049 (-0.131-0.034) | Dominated (-\$254,762/QALY) |
| Altering readmission costs (accounting for LOS) | \$19,165 (-\$2,689-\$41,019) | -0.049 (-0.131-0.034) | Dominated (-\$392,013/QALY) |
| Adjusting for baseline covariates | \$15,427 (-\$2,358-\$33,211) | -0.063 (-0.139-0.012) | Dominated -\$243,178/QALY (-\$670,677to -\$98,771) |
| GLM adjusting for baseline covariates | \$15,274 (-\$1,830-\$32,377) | -0.063 (-0.139-0.012) | Dominated -\$240,765/QALY (-\$567,752 to -\$51,591) |
| Including entire cohort for QALYs (n=1377) | \$13,044 (-\$5,314-\$31,401) | 0.009 (-0.021-0.040) | \$1,416,342/QALY |

CI=confidence interval; LTC=long term care; LOS=length of stay; AUD=Australian dollars; QALYs= quality-adjusted life years; ICER=incremental cost-effectiveness ratio; GLM=generalised linear model

¹ 95% CIs presented when they are able to be defined

eTable 8 Emergency department staff time and costs

| | Staff member | Time | Cost (2014 AUD) | Source |
|---|-------------------------|-----------------------|-----------------|---|
| Nursing activities | | | | |
| Bedside nursing care (including assessment, observation and routine management) | Nurse | 50% of patient ED LOS | Based on ED LOS | Expert opinion |
| Medical activities | | | | |
| Initial treating clinician bedside evaluation | Registrar | 30min | \$32.98 | IHPA Emergency care costing and classification project report- Emergency care clinician time consensus study report of final results ¹ |
| Initial treating clinician synthesis and documentation | Registrar | 24min | \$26.38 | |
| Initial senior assessment (70% of cases) | Consultant ED clinician | 10 min | \$16.59 | |
| Additional treating clinician bedside evaluation, synthesis and documentation (75% of cases), | Registrar | 30min | \$24.74 | |
| External clinician phone consultation (80% of cases) | Registrar | 12min | \$10.55 | |
| Third party conversations (50% of cases) | Registrar | 12 min | \$6.60 | |
| External clinician in-person consultation (60% of cases) | Registrar | 36 min | \$23.74 | |
| Senior review – patient examination (62.5% of cases) | Consultant ED clinician | 10 min | \$14.81 | |
| Treating clinician summation and handover | Registrar | 24min | \$26.38 | |

ED=emergency department; LOS=length of stay; AUD=Australian dollars

eTable 9 Emergency department staff hourly wages

| Staff type | Hourly wage (2014 AUD) ¹ | Source |
|--------------------|-------------------------------------|--|
| Medical consultant | \$142.23 | Average of 2014 (where available) enterprise agreement salaries in WA, NSW, Victoria and SA ²⁻⁹ |
| Medical registrar | \$65.95 | |
| Medical resident | \$46.82 | |
| Nurse | \$43.88 | |

AUD=Australian dollars

¹ Includes 20% on-costs

eTable 10 ICU, ward and allied health staffing costs

| Staff type | Unit cost (2014 AUD) | Source |
|--|----------------------|--|
| Daily ICU staff cost | \$3475.51 per day | ANZICS CCR Survey 2013/2014; with an additional 20% overheads |
| Daily ward staff cost | \$618.29 per day | Alfred hospital average ward cost |
| Allied health consultations | | |
| Physiotherapist/ Occupational therapist/Speech therapist/Social worker/Orthotist | \$43.82 | National 2014 (where available) enterprise agreement salary ¹⁰ with an additional 20% overheads |
| Dietician | \$46.66 | Fair work commision ¹¹ with an additional 20% overheads |
| Pharmacist | \$46.49 | Fair work commision ¹¹ with an additional 20% overheads |
| Psychologist | \$55.12 | Fair work commision ¹¹ with an additional 20% overheads |
| Other consultation | | |
| Specialist nursing (e.g. stomal therapist) | \$47.04 | Fair work Australia ⁵ with an additional 20% overheads |
| Interpreter | \$33.73 | Fair work commision ¹⁰ with an additional 20% overheads |
| Pastoral care | \$26.00 | Fair work commision ¹⁰ with an additional 20% overheads |
| Rehabilitation consultant | \$49.93 | Fair work commision ¹⁰ with an additional 20% overheads |

AUD=Australian dollars; ICU=intensive care unit

eTable 11 Procedure unit costs

| Procedure type | Staffing cost¹ (2014 AUD) | Other costs² (2014 AUD) |
|---------------------------------------|---|---|
| Catheter and line insertions | | |
| ScvO ₂ catheter | \$65.89 | \$743.76 |
| CVC | \$54.92 | \$176.80 |
| Arterial line | \$34.77 | \$140.93 |
| Peripheral IV line | \$12.81 | \$5.44 |
| Vascath | \$67.02 | \$189.79 |
| Swan Ganz sheath | \$54.92 | \$101.99 |
| PiCCO | \$54.92 | \$315.03 |
| PICC line | \$54.92 | \$242.39 |
| Intraosseous needle | \$3.30 | \$101.27 |
| Subcutaneous cannula | \$3.66 | \$2.01 |
| Nasogastric tube | \$18.30 | \$11.14 |
| Indwelling catheter | \$10.97 | \$21.36 |
| Suprapubic catheter | \$31.12 | \$56.00 |
| Intercostal catheter | \$54.92 | \$94.02 |
| Faecal management system | \$10.97 | \$211.70 |
| Other procedures | | |
| Intubation | \$124.46 | \$69.14 |
| Ventilator set up | \$13.53 | \$109.98 |
| Non-invasive ventilator set up | \$53.41 | \$135.90 |
| Haemodialysis set up ³ | \$39.86 | \$320.90 |
| ECMO set up ⁴ | N/A (not inserted in ED) | \$3000.89 |
| Percutaneous tracheostomy insertion | \$180.96 | \$330.31 |
| EEG ⁵ | N/A | \$123.10 |
| Bronchoscopy ⁵ | N/A | \$178.05 |
| Pulmonary function tests ⁵ | N/A | \$138.65 |

CVC=central venous catheter; IV=intravenous; ED=emergency department; ECMO=extracorporeal membrane oxygenation; EEG=electroencephalogram; AUD=Australian dollars

¹ All staffing costs were based on (1) or convenience sample of critically care trained medical and nursing staff if not available in (1); Staffing costs were only applied for ED procedures

² All other costs were the sum of the cost of consumables and the capital equipment costs, unless specified below

³ Ongoing haemodialysis costs based on dialysate and replacement fluid volumes, circuit and catheter changes and regional anticoagulation doses

⁴ Ongoing ECMO costs based on circuit and catheter changes

⁵ EEG cost based on MBS item number 11000, bronchoscopy cost based on MBS item number 41889, and pulmonary function test cost based on MBS item number 11503¹²

eTable 12 Additional costs associated with EGDT

| | Description | Cost (2014 AUD) | Source |
|--|---|--|---|
| PreSep™ ScvO₂ catheter | N/A | \$429.38 | Manufacturer (Edwards Lifesciences) |
| ScvO₂ monitor | Monitor cost of \$13,598 ¹ , lifespan of 5 years, 2 monitors per ED with 35 eligible patients per year | \$179.48 per patient | Manufacturer (Edwards Lifesciences) |
| PreSep™ ScvO₂ catheter insertion | 30 minutes medical, 45 minutes nursing, catheter and consumables | \$199.21 | Expert opinion, average site consumable cost and salaries as per eTable 9 |
| ScvO₂ monitor set-up | 30 minutes nursing time | \$21.94 | Expert opinion and salaries as per eTable 9 |
| Nursing time during EGDT delivery | Additional 10 minutes per hour of EGDT delivery | Based on EGDT delivery time (up to 6 hours) and rate of \$43.88/hour | Expert opinion and salaries as per eTable 9 |
| EGDT training | 30 minutes of training (yearly for residents, 2 yearly for nurses and registrar, 5 yearly for consultants) | \$29.76 per patient | Expert opinion and salaries as per eTable 9 |

AUD=Australian dollars; EGDT=early goal directed therapy

¹ Monitor cost includes both Vigileo monitor and oximetry optical module

eTable 13 Capital equipment costs

| Equipment | Cost (2014 AUD) | Source |
|---------------------------------|--|--------------------------|
| Ultrasound | \$8.96 per US in ED \$10.54 per US in ICU | Commercial in confidence |
| Ventilator | \$21.32 per ventilated day | Commercial in confidence |
| Non-invasive ventilator | \$23.07 per non-invasively ventilated day | Commercial in confidence |
| Haemodialysis machine | \$18.49 per day of CRRT | Commercial in confidence |
| IV pump | \$5.51 per ICU day | Commercial in confidence |
| ECMO machine | \$257.59 per day of ECMO | Alfred hospital |
| ICU bed | \$18.46 per ICU day | Commercial in confidence |
| ICU chair | \$0.71 per ICU day | Commercial in confidence |
| Bedside resuscitation equipment | \$0.85 per ICU day | Alfred hospital |

AUD=Australian dollars; IV=intravenous; ECMO=extracorporeal membrane oxygenation; ED=emergency department; ICU=intensive care unit; US=ultrasound; CRRT=continuous renal replacement therapy

eTable 14 Post discharge unit costs

| Post discharge healthcare use | Unit Cost (AUD 2014) | Source |
|--------------------------------------|-----------------------------|---|
| Inpatient healthcare use | | |
| Acute care readmissions | Based on AR-DRG | NHCDC Round 18 cost report ¹³ |
| Rehabilitation | \$909.72 per day | IHPA National efficient price determination 2013-14 ²⁰ |
| High level long term care | \$845.31 per day | NHCDC Round 18 cost report , AN-SNAP class 3-504 (Overnight Maintenance Nursing Home Type, RUG-ADL 11-18) ¹³ |
| Low level long term care | \$365.99 per day | NHCDC Round 18 cost report, AN-SNAP class 3-511 (Overnight Maintenance Long term care, RUG-ADL 4-9) ¹³ |
| Outpatient healthcare use | | |
| Medical | | |
| Medical specialist | \$85.55 | MBS item number 104 ¹² |
| General practitioner | \$36.30 | MBS item number 23 ¹² |
| Nursing | | |
| Nursing | \$20.95 | MBS item number 82205 ¹² |
| Allied health | | |
| Physiotherapy | \$62.25 | MBS item number 10960 ¹² |
| Occupational therapy | \$62.25 | MBS item number 10958 ¹² |
| Speech therapy | \$62.25 | MBS item number 10970 ¹² |
| Dietetics | \$62.25 | MBS item number 10954 ¹² |
| Psychology | \$62.25 | MBS item number 10968 ¹² |
| Social work | \$62.25 | MBS item number 10956 ¹² |
| Chiropractic/Osteopathy | \$62.25 | MBS item number 10964/10966 ¹² |
| Podiatry | \$62.25 | MBS item number 10962 ¹² |
| Audiology | \$62.25 | MBS item number 10952 ¹² |
| Optometry | \$62.25 | MBS item number 10905 ¹² |
| Prosthetics | \$62.25 | Based on allied health MBS fees above |
| Carer | \$31.36 | Carers Australia ²¹ |

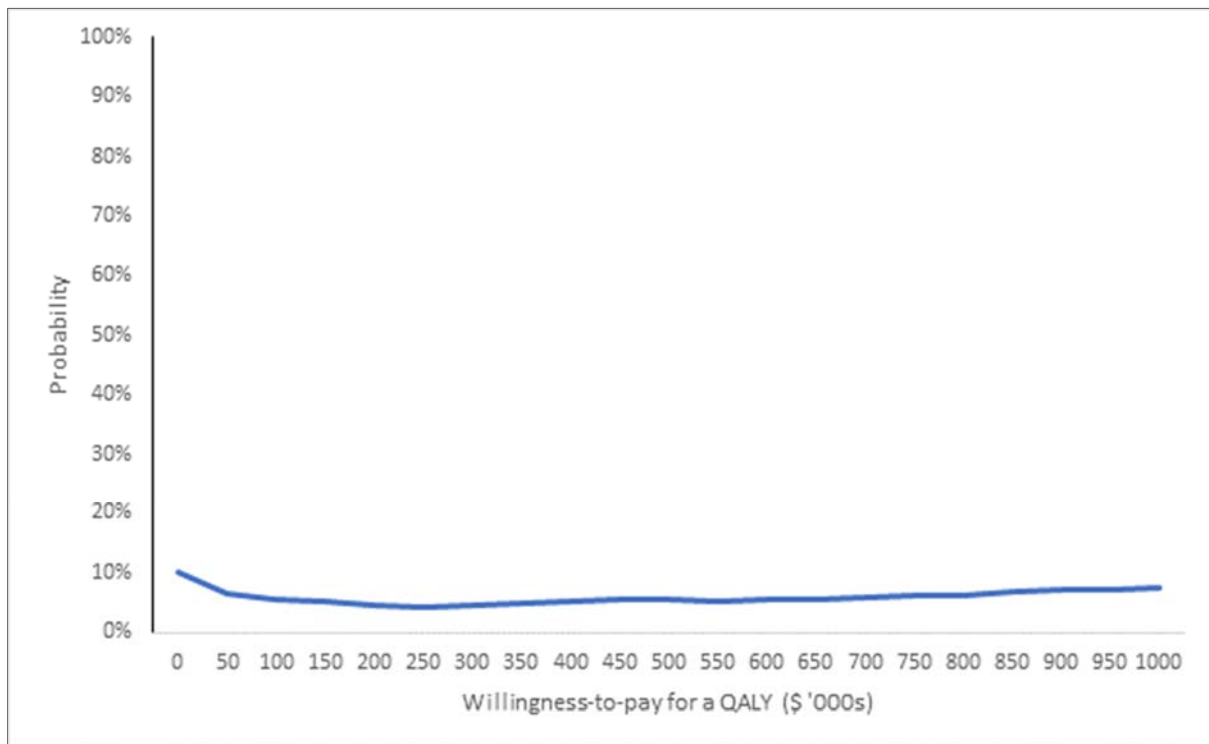
AUD=Australian dollars; AR-DRG=Australian-defined Diagnoss Related Group; IHPA=Independent Hospital Pricing Authority; NHCDC=National Hospital Costs Data Collection; RUG-ADL=Resource Utilisation Group-Activities of Daily Living; MBS=Medicare Benefits Schedule

eTable 14 continued Post discharge unit costs

| Post discharge healthcare use | Unit Cost (AUD 2014) | Source |
|--------------------------------------|---------------------------------|---|
| Other | | |
| Cardiac rehabilitation | \$220 | NHCDC Round 18 (Tier 2 class) ¹³ |
| Pulmonary rehabilitation | \$130 | NHCDC Round 18 (Tier 2 class) ¹³ |
| Dentist | \$85.55 | MBS item number 51700 ¹² |
| Radiotherapy | \$713 | NHCDC Round 18 (Tier 2 class) ¹³ |
| Pathology testing | \$118 | NHCDC Round 18 (Tier 2 class) ¹³ |
| Outpatient radiology | | |
| CT | \$159 | NHCDC Round 18 (Tier 2 class) ¹³ |
| US | \$111.30 | MBS item number 55036 ¹² |
| Doppler scan | \$57.75 | MBS item number 11602 ¹² |
| PET – whole body | \$953 | MBS item number 61523-61632 ¹² |
| MRI | \$658 | NHCDC Round 18 (Tier 2 class) ¹³ |
| Chest X-ray | \$35.35 | MBS item number 58500 ¹² |

AUD=Australian dollars; NHCDC=National Hospital Costs Data Collection; MBS=Medicare Benefits Schedule

eFigure 1 Cost-effectiveness acceptability curve



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