**Supplementary Digital Content 2**

**Table S1 Baseline characteristics of participants for whom HRQoL measures were completed (responders) or not completed (non-responders) at baseline**

|  |  |
| --- | --- |
| **Characteristic** | **Baseline** |
| **Responders** **(n=803)** | **Non-responders (n=788)** |
| Male gender (n(%))\* | 491 (62.3) | 459 (57.2) |
| Age | 62.8 ± 16.0 | 63.0 ± 16.9 |
| APACHE II score\*\* | 14.9 ± 6.4 | 16.3 ± 6.6 |
| Mechanical ventilation (n(%)) | 74 (9.2) | 61 (7.7) |
| Vasopressor infusion (n(%)) | 173 (22.0) | 173 (21.5) |
| Charlson comorbidity (1 or more)\*\*\* | 423 (53.7%) | 481 (59.9%) |

APACHE II= Acute Physiology And Chronic Health Evaluation II

\*p=0.04

\*\*p<0.001

\*\*\*p=0.01

**Table S2 Baseline characteristics of participants for whom HRQoL measures were completed (responders) or not completed (non-responders) at 6 and 12 months**^

|  |  |  |
| --- | --- | --- |
| **Baseline characteristic** | **6 months** | **12 months** |
| **Responders** | **Non-responders** | **Responders** | **Non-responders** |
| n | 1013 | 234 | 940 | 240 |
| Male gender (n(%)) | 602 (59.4) | 137 (58.6) | 550 (58.5) | 144 (60.0) |
| Age (years) | 62.1 ± 16.0 | 58.5 ± 18.5\* | 61.6 ± 16.1 | 58.5 ± 18.4\*\* |
| APACHE II score | 14.5 ± 6.1 | 14.8 ± 6.2 | 14.3 ± 6.1 | 14.6 ± 6.2 |
| Baseline mechanical ventilation (n(%)) | 73 (7.2) | 20 (8.6) | 67 (7.1) | 22 (9.2) |
| Baseline vasopressor infusion (n(%)) | 204 (20.1) | 48 (20.5) | 181 (19.3) | 50 (20.8) |
| Charlson comorbidity (1 or more) (n(%)) | 533 (52.6) | 125 (53.4) | 470 (50.0) | 131 (54.6) |

^excludes those know to be deceased at each timepoint; incomplete considered non-responders as no assumptions made for missing data

APACHE II= Acute Physiology And Chronic Health Evaluation II

\*p=0.003

\*\*p=0.01

**Table S3 EuroQOL-5D-3L quality of life assessment tool domains at baseline**

|  |  |
| --- | --- |
| **EQ-5D-3L Domain** | **Baseline** |
| **EGDT****n=417** | **UC****n=371** | **p-value** |
| Mobility, N(%) |  |  | 0.72 |
|  | I have no problems in walking around | 241 (57.8) | 208 (56.1) |  |
|  | I have some problems in walking around | 162 (38.9) | 153 (41.2) |
|  | I am confined to bed | 14 (3.4) | 10 (2.7) |
| Selfcare, N(%) |  |  | 0.77 |
|  | I have no problems with personal care | 315 (75.5) | 272 (73.3) |  |
|  | I have some problems washing or dressing myself | 82 (19.7) | 79 (21.3) |
|  | I am unable to wash or dress myself | 20 (4.8) | 20 (5.4) |
| Activity, N(%) |  |  | 0.35 |
|  | I have no problems with performing my usual activities | 237 (56.8) | 209 (56.3) |  |
|  | I have some problems with performing my usual activities | 139 (33.3) | 114 (30.7) |
|  | I am unable to perform my usual activities | 41 (9.8) | 48 (12.9) |
| Pain, N(%) |  |  | 0.06 |
|  | I have no pain or discomfort | 191 (45.8) | 165 (44.5) |  |
|  | I have moderate pain or discomfort | 197 (47.2) | 162 (43.7) |
|  | I have extreme pain or discomfort | 29 (7.0) | 44 (11.9) |
| Anxiety and depression, N(%) |  |  | 0.45 |
|  | I am not anxious or depressed | 248 (59.5) | 226 (60.9) |  |
|  | I am moderately anxious or depressed | 150 (36.0) | 122 (32.9) |
|  | I am extremely anxious or depressed | 19 (4.6) | 23 (6.2) |

EQ-5D-3L=EuroQOL-5D-3L quality of life assessment tool, EGDT=early goal directed therapy, UC=usual care

**Table S4** **Short Form 36 domains at baseline**

|  |  |  |
| --- | --- | --- |
| **SF-36 Domain** | **Baseline** | **Age-matched Australian normative valuesc** |
| **EGDTa** | **UCb** | **p-value** |
| Physical functioning | 37.6 ± 14.4 | 36.5 ± 14.8 | 0.33 | 47.4 ± 10.7 |
| Role physical | 40.6 ± 13.6 | 39.7 ± 13.9 | 0.43 | 47.5 ± 12.0 |
| Bodily pain | 47.6 ± 12.4 | 45.9 ± 13.7 | 0.07 | 47.3 ± 10.4 |
| General health | 40.1 ± 12.6 | 38.9 ± 12.4 | 0.21 | 47.4 ± 11.9 |
| Vitality | 45.7 ± 12.7  | 44.3 ± 12.6 | 0.16 | 49.0 ± 10.9 |
| Social functioning | 41.9 ± 13.3 | 40.8 ± 14.3 | 0.33 | 49.3 ± 11.1 |
| Role emotional | 43.2 ± 14.8 | 42.1 ± 15.8 | 0.31 | 49.2 ± 11.5 |
| Mental health | 48.0 ± 12.2 | 46.0 ± 12.9 | 0.03 | 49.4 ± 11.2 |

SF-36=Short Form 36, EGDT=early goal directed therapy, UC=usual care

Results presented as mean ± SD

a n ranges from 366 for physical functioning to 376 for bodily pain

b n ranges from 316 for physical functioning to 332 for role physical

c Age-matched Australian population for mean (SD) age 62.9 years (16.5) of patients with baseline data; differences between each group and populations norms all p<0.001

**Table S5. Short Form 36 domain scores at 6 and 12 months**

|  |  |  |  |
| --- | --- | --- | --- |
| **SF-36 Domain** | **6 monthsa** | **12 monthsb** | **Populations Normsc** |
| **EGDT** | **UC** | **p-value** | **EGDT** | **UC** | **p-value** |
| Physical functioning | 36.5 ± 13.6  | 37.1 ± 13.3 | 0.66 | 38.2 ± 13.7 | 37.3 ± 13.6 | 0.46 | 47.4 ± 10.7 |
| Role physical | 37.7 ± 12.7 | 39.1 ± 12.6 | 0.21 | 39.6 ± 12.8 | 38.6 ± 13.7 | 0.40 | 47.5 ± 12.0 |
| Bodily pain | 46.0 ± 12.2 | 45.4 ± 12.4 | 0.58 | 45.7 ± 12.1 | 44.3 ± 12.6 | 0.20 | 47.3 ± 10.4 |
| General health | 38.9 ± 13.1 | 38.9 ± 12.2 | 0.99 | 40.5 ± 12.6 | 39.1 ± 12.0 | 0.21 | 47.4 ± 11.9 |
| Vitality | 44.7 ± 11.4 | 45.8 ± 11.5 | 0.25 | 46.4 ± 11.9 | 45.3 ± 11.6 | 0.32 | 49.0 ± 10.9 |
| Social functioning | 41.4 ± 13.9 | 40.5 ±13.6 | 0.46 | 42.7 ± 13.0 | 41.0 ± 14.2 | 0.17 | 49.3 ± 11.1 |
| Role emotional | 40.1 ± 14.8 | 41.5 ± 14.8 | 0.29 | 41.8 ± 14.9 | 40.2 ± 15.8 | 0.27 | 49.2 ± 11.5 |
| Mental health | 47.5 ± 11.7 | 47.2 ± 12.3 | 0.79 | 47.8 ± 11.3 | 47.0 ± 12.6 | 0.43 | 49.4 ± 11.2 |

SF-36=Short Form 36; EGDT=early goal directed therapy; UC=usual care

Results presented as mean ± sd

an for individual domains at 6 months ranges from 254/602 survivors for physical functioning in the EGDT group to 270/602 survivors for bodily pain in the usual care group

bn for individual domains at 12 months ranges from 234/556 survivors for physical functioning in the EGDT group to 269/548 survivors for bodily pain in the usual care group

cAustralian population norms for age 55-64 years (15)

**Table S6 Changes in HR-QoL from baseline to 12 months**

|  |  |  |
| --- | --- | --- |
| **HR-QoL measure** | **EGDT** | **UC** |
| **Baseline** | **12 months** | **Difference** | **p-value** | **Baseline** | **12 months** | **Difference** | **p-value** |
| EQ VASa | 66.80 ± 23.00 | 70.28 ± 19.30 | -3.48 ± 24.06 | 0.01 | 61.47 ± 24.11 | 68.60 ± 20.04 | -7.14 ± 24.77 | <0.0001 |
| EQ-5D-3L utility scoreb | 0.71 ± 0.31 | 0.69 ± 0.30 | 0.02 ± 0.30 | 0.39 | 0.66 ± 0.34 | 0.66 ± 0.32 | 0.00 ± 0.34 | 0.93 |
| SF-36 MCSc | 50.15 ± 11.16 | 47.39 ± 12.93 | 2.75 ± 12.48 | 0.01 | 47.42 ± 13.10 | 47.60 ± 13.61 | -0.17 ± 13.89 | 0.89 |
| SF-36 PCSc | 41.75 ± 11.86 | 40.08 ± 12.58 | 1.67 ± 10.55 | 0.07 | 41.12 ± 13.71 | 39.99 ± 12.71 | 1.13 ± 9.87 | 0.22 |
| SF-36 domainsd |  |  |  |  |  |  |  |  |
|  Physical functioning | 38.95 ± 13.53 | 39.05 ± 13.53 | -0.11 ± 11.70 | 0.91 | 38.50 ± 14.66 | 38.35 ± 13.71 | 0.15 ± 10.55 | 0.87 |
|  Role physical | 43.19 ± 12.49 | 40.06 ± 12.32 | 3.12 ± 12.68 | 0.002 | 41.57 ± 13.57 | 38.83 ± 13.70 | 2.74 ± 14.13 | 0.02 |
|  Bodily pain | 49.00 ± 11.41 | 46.45 ± 11.47 | 2.55 ± 11.97 | 0.006 | 46.78 ± 13.79 | 44.70 ±12.21 | 2.08 ±12.23 | 0.04 |
|  General health | 42.02 ± 12.98 | 40.74 ± 12.61 | 1.28 ± 10.68 | 0.13 | 40.10 ± 12.36 | 40.07 ± 11.78 | 0.04 ± 11.20 | 0.97 |
|  Vitality | 47.46 ± 11.79 | 46.52 ± 11.21 | 0.94 ± 11.23 | 0.28 | 44.80 ± 13.03 | 45.25 ± 11.85 | -0.45 ± 11.83 | 0.65 |
|  Social functioning | 44.51 ± 12.53 | 43.60 ± 12.71 | 0.91 ± 12.16 | 0.33 | 42.59 ± 13.78 | 41.84 ± 13.89 | 0.75 ± 14.57 | 0.52 |
|  Role emotional | 46.16 ± 12.44 | 43.19 ± 14.14 | 2.97 ± 14.22 | 0.009 | 43.57 ± 14.33 | 41.59 ± 15.86 | 1.98 ± 17.22 | 0.16 |
|  Mental health | 50.24 ± 10.45 | 47.74 ± 11.21 | 2.20 ± 10.69 | 0.003 | 47.73 ± 11.96 | 47.33 ± 12.22 | 0.41 ± 11.51 | 0.67 |
| AQoL utility scoree | 0.64 ± 0.29 | 0.61 ± 0.27 | 0.02 ± 0.26 | 0.28 | 0.56 ± 0.31 | 0.52 ± 0.32 | 0.04 ± 0.28 | 0.12 |

Results presented as mean ± sd

EGDT=early goal directed therapy, UC=usual care, EQ VAS=EQ visual analogue score, EQ-5D-3L= EuroQOL-5D-3L quality of life assessment tool, SF-36=Short Form 36, PCS=physical component score, MCS=mental component score, AQOL= Assessment of Quality of Life 4D

a n=296 for EGDT and n=257 for UC

b n=304 for EGDT and n=262 for UC

c n=133 for EGDT and n=116 for UC

d n for individual domains at 6 months ranges from 140 for physical functioning in the EGDT group to 172 for bodily pain in the UC group

e n=151 for EGDT and n=139 for UC

**Table S7 Cox multivariate model duration of survival to 12 months**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Comparator** | **Hazard Ratio (95% CI)** | **p-value** |
| Study treatment  | EGDT vs UC | 0.97 (0.80-1.17) | 0.73 |
| Age | 1 year increase | 1.02 (1.01-1.02) | <0.001 |
| APACHE II score | 1 unit increase | 1.10 (1.08-1.11) | <0.001 |
| Country  | Australia (index)New ZealandIrelandHong KongFinland | 0.90 (0.60-1.34)1.53 (0.38-6.15)1.04 (0.59-1.82)0.87 (0.46-1.66) | 0.590.550.910.68 |
| Mechanical ventilation at randomization  | Ventilated vs not | 1.15 (0.82-1.60) | 0.41 |
| SBP at randomization | SBP<90mmHg vs ≥90mmHg  | 1.02 (0.83-1.24) | 0.15 |

CI=confidence interval, EGDT=early goal directed therapy, UC=usual care, APACHE II= Acute Physiology And Chronic Health Evaluation II, SBP=systolic blood pressure

**Table S8 Logistic regression model for 12 month mortality**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Comparator** | **Odds Ratio (95% CI)** | **p-value** |
| Study treatment  | EGDT vs UC | 0.98 (0.76-1.24) | 0.84 |
| Age | 1 year increase | 1.02 (1.01-1.03) | <0.001 |
| APACHE II score | 1 unit increase | 1.12 (1.10-1.14) | <0.001 |
| Country  | Australia (index)New ZealandIrelandHong KongFinland | 0.78 (0.49-1.24)1.53 (0.26-9.16)1.36 (0.02-2.95)0.84 (0.40-1.79) | 0.300.640.440.65 |
| Mechanical ventilation at randomization  | Ventilated vs not | 1.16 (0.72-1.73) | 0.62 |
| SBP at randomization | SBP<90mmHg vs ≥90mmHg  | 0.93 (0.72-1.20) | 0.57 |

CI=confidence interval, EGDT=early goal directed therapy, UC=usual care, APACHE II= Acute Physiology And Chronic Health Evaluation II, SBP=systolic blood pressure

**Table S9 Linear regression model for 12 month HRQoL among survivors (EQ5D-5L utility score)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Comparator** | **Coefficient (95% CI)** | **p-value** |
| Study treatment  | EGDT vs UC | 0.01 (-0.03 to 0.05) | 0.57 |
| Age | 1 year increase | -0.002 (-0.004 to -0.0007) | 0.003 |
| APACHE II score | 1 unit increase | -0.003 (-0.007 to 0.0002) | 0.07 |
| Country  | Australia (index)New ZealandIrelandHong KongFinland | 0.02 (-0.06 to 0.09)0.14 (-0.19 to 0.46)0.08 (-0.07 to 0.23)0.11 (-0.006 to 0.22) | 0.670.410.320.06 |
| Mechanical ventilation at randomization  | Ventilated vs not | 0.002 (-0.09 to 0.09) | 0.96 |
| SBP at randomization | SBP<90mmHg vs ≥90mmHg  | 0.02 (-0.02 to 0.07) | 0.28 |

CI=confidence interval, EGDT=early goal directed therapy, UC=usual care, APACHE II= Acute Physiology And Chronic Health Evaluation II, SBP=systolic blood pressure

**Table S10 Mortality and HR-QoL stratified by Charlson co-morbidity score**

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcome** | **Charlson comorbidity score=0** | **Charlson comorbidity score=1** | **Charlson comorbidity score≥2** |
| **EGDT (n=335)** | **UC (n=352)** | **p-value** | **EGDT (n=188)** | **UC (n=192)** | **p-value** | **EGDT (n=270)** | **UC (n=254)** | **p-value** |
| 90-day mortality | 48/334 (14.4%) | 43/351 (12.3%) | 0.41 | 36/188 (19.2% | 36/191 (18.9%) | 0.94 | 63/270 (23.3%) | 71/254 (28.0) | 0.23 |
| 6-month mortality | 51/325 (15.7%) | 47/340 (13.8%) | 0.50 | 38/182 (20.9%) | 43/188 (22.9%) | 0.64 | 79/263 (30.0%) | 86/250 (34.4%) | 0.29 |
| 1-year mortality | 54/316 (17.1%) | 54/331 (16.3%) | 0.79 | 48/182 (26.4%) | 53/185 (28.7%) | 0.63 | 97/257 (37.7%) | 105/244 (43.0%) | 0.23 |
| EQ VASa b |  |  |  |  |  |  |  |  |  |
|  | Baseline | 71.54 ± 22.92 | 65.84 ± 23.87 | 0.04 | 60.79 ± 24.11 | 56.22 ± 25.51 | 0.30 | 62.92 ± 20.03 | 57.33 ± 22.13 | 0.12 |
|  | 12 months | 74.46 ± 17.41 | 72.09 ± 19.84 | 0.28 | 66.39 ± 20.61 | 64.18 ± 20.54 | 0.55 | 65.45 ± 20.01 | 65.50 ± 19.09 | 0.99 |
| EQ-5D-3L utility scorea c |  |  |  |  |  |  |  |  |  |
|  | Baseline | 0.73 ± 0.32 | 0.69 ± 0.35 | 0.26 | 0.68 ± 0.31 | 0.64 ± 0.33 | 0.43 | 0.67 ± 0.31 | 0.62 ± 0.34 | 0.33 |
|  | 12 months | 0.74 ± 0.28 | 0.71 ± 0.29 | 0.41 | 0.65 ± 0.31 | 0.62 ± 0.36 | 0.55 | 0.63 ± 0.32 | 0.59 ± 0.34 | 0.42 |
| SF-36 PCSa d |  |  |  |  |  |  |  |  |  |
|  | Baseline | 46.62 ± 10.82 | 46.18 ± 12.12 | 0.83 | 36.70 ± 10.82 | 35.58 ± 15.40 | 0.40 | 37.14 ± 11.11 | 37.69 ± 11.92 | 0.84 |
|  | 12 months | 45.54 ± 10.66  | 43.95 ± 11.88 | 0.43 | 35.09 ± 12.50 | 33.17 ± 12.57 | 0.59 | 34.40 ± 11.87 | 37.90 ± 12.04 | 0.22 |
| SF-36 MCSa d |  |  |  |  |  |  |  |  |  |
|  | Baseline | 53.26 ± 9.46 | 44.84 ± 13.31 | <0.001 | 47.35 ± 12.41 | 49.95 ± 13.45 | 0.47 | 46.89 ± 11.67 | 47.35 ± 12.41 | 0.26 |
|  | 12 months | 50.61 ± 11.34 | 48.41 ± 12.36 | 0.30 | 41.89 ± 15.89 | 42.87 ± 14.64 | 0.82 | 46.00 ± 11.62 | 41.89 ± 15.89 | 0.28 |
| AQoL utility scorea e |  |  |  |  |  |  |  |  |  |
|  | Baseline | 0.70 ± 0.28 | 0.60 ± 0.31 | 0.04 | 0.54 ± 0.29 | 0.47 ± 0.28 | 0.42 | 0.59 ± 0.29 | 0.54 ± 0.32 | 0.42 |
|  | 12 months | 0.71 ± 0.23 | 0.61 ±0.31 | 0.02 | 0.53 ± 0.30 | 0.35 ± 0.32 | 0.04 | 0.51 ± 0.26 | 0.48 ± 0.28 | 0.64 |

Results presented as number (%) or mean ± sd

EGDT=early goal directed therapy, EQ VAS=EQ visual analogue score, EQ-5D-3L= EuroQOL-5D-3L quality of life assessment tool, SF-36=Short Form 36, PCS=physical component score, MCS=mental component score, AQOL= Assessment of Quality of Life 4D

a All HR-QoL scores for patients who had baseline and 12 month data available

b EQ VAS scores for n=154, 66 and 84 for Charlson scores of 0,1 and ≥2 respectively in EGDT group; and n=135, 57 and 70 in usual care group

c EQ-5D-3L utility scores for n=154, 66 and 84 for Charlson scores of 0,1 and ≥2 respectively in EGDT group; and n=135, 57 and 70 in usual care group

d SF36 PCS and MCS scores for n=66, 29 and 38 for Charlson scores of 0,1 and ≥2 respectively in EGDT group; and n=58, 23 and 35 in usual care group

e AQoL utility scores for n=76, 31 and 44 for Charlson scores of 0,1 and ≥2 respectively in EGDT group; and n=73, 23 and 43 in usual care group