**ELECTRONIC SUPPLEMENTARY APPENDIX**

**Trial Personnel (alphabetically by institution)**

Austin Health, Melbourne, VIC, R. Bellomo, G. Eastwood, L. Peck, H. Young

Dandenong Hospital, Melbourne, VIC, L. Bulfin, N. Hart, K. Shepherd, S. Vij; Derriford Hospital, Derriford, UK, S. Dickson, E. Elloway, C. Ferguson, R. Jackson, P. MacNaughton, M. Marner, R. Squire, S. Waddy, P. Wafer, J. Welbourne

Monash Medical Centre, Melbourne, VIC, D. Bhatia, L. Bulfin, S. Elliot, P. Galt, K. Lavrans, P. Ritchie, A. Wang, M. Balachandran, P. Banneheke, Y. Shehabi

Wellington Regional Hospital, Wellington, NZ, R. Sol Cruz, D. Dinsdale, S. Edney, C. Firkin, F. FitzJohn, K. Grayson, G. Hill, A. Hunt, S. Hurford, G. Jones, H. Judd, C. Latimer-Bell, C. Lawrence, E. Lesona, L. Navarra, Y. Robertson, H. Smellie, AM. Vucago, J. Wright, P. Young

**eMETHODS**

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| **Table S1:** Data collected specifically for this analysis | |
| **Data** | **Description** |
| **Baseline data** | |
| Baseline temperature | Most recent temperature before randomisation |
| **Daily data** | |
| Six hourly temperatures | For five days post randomisation or until discharge or death |
| Highest daily temperature | For five days post randomisation or until discharge or death |
| Paracetamol | Daily dose of (grams) while in ICU |
| **Outcome data** | |
| IV Antimicrobials | Days patient received IV antimicrobials in ICU for five days post randomisation or until discharge or death |
| Blood cultures | Number of sets of blood cultures taken for five days post randomisation or until discharge or death |
| Positive blood cultures | Number of positive blood cultures reported |

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| **Table S2:** Eligibility criteria |
| **Full inclusion criteria** |
| Subject has been intubated and is receiving mechanical ventilation |
| The treating clinician expects that the patient will remain intubated until the day after tomorrow (unlikely to be extubated the following day) |
| The patient requires immediate ongoing sedative medication for comfort, safety,  and to facilitate the delivery of life support measures |
| **Full exclusion criteria** |
| Age less than 18 years |
| Patient is pregnant and/or lactating |
| Has been intubated (excluding time spent intubated within an operating theatre or transport) for greater than 12 hours in an intensive care unit |
| Proven or suspected acute primary brain lesion such as traumatic brain injury, |
| Proven or suspected spinal cord injury or other pathology that may result in  permanent or prolonged weakness |
| Admission as a consequence of a suspected or proven drug overdose or burns |
| Administration of ongoing neuromuscular blockade |
| Mean arterial blood (MAP) pressure that is less than 50 mmHg despite adequate resuscitation and vasopressor therapy at time of randomisation |
| Heart rate less than 55 beats per minute unless the patient is being treated with a beta-blocker or a high grade atrio-ventricular block in the absence of a functioning pacemaker |
| Known sensitivity to any of the study medications or the constituents of propofol (egg, soya or peanut protein) |
| Acute fulminant hepatic failure |
| Patient has been receiving full time residential nursing care |
| Death is deemed to be imminent or inevitable during this admission and either the attending physician, patient or substitute decision maker is not committed to active treatment |
| Patient has an underlying disease that makes survival to 90 days unlikely |
| Patient has been previously enrolled in the SPICE study |

**Neuroleptic Drugs**

The following medications that were given to patients in the ICU were defined as neuroleptic drugs for the purposes of reporting in this sub-study: droperidol, olanzapine, quetiapine, risperidone, haloperidol.

**Evaluating the effect of baseline values**

We ran two additional analyses to determine the sensitivity of high or low baseline values:

1. Repeat measures analysis of variance for average and highest temperatures to examine changes from baseline

2. Sensitivity analysis for time to first hyperthermia excluding patients with baseline temperatures < 35°C and >38.3°C.

**Post Hoc Exploratory Analysis**

Given the competing risk of death and ICU discharge, analysis of a definitive dose-response relationship is problematic. To explore the relationship between daily administration of dexmedetomidine and highest daily temperature we conducted post-hoc exploratory analyses. Using mixed linear modelling, a per-protocol and dose-response analysis were performed, adjusting for the following covariates: age, baseline temperature, diagnosis, daily ventilation, neuromuscular blockade, neuroleptics, paracetamol, positive blood culture, Weight >100kg, active mobilisation, day, diazepam usage, propofol usage and renal replacement therapy.

**eRESULTS**

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| C:\Users\mickb\SGPlot1.png  C:\Users\mickb\SGPlot2.png | | |
|  | **Figure S1.** Distribution for mean daily temperature (A) and peak daily temperature (B) |  |
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| **Table S3.** Multivariate analysis for time to temperature ≥38.3°C | | | | |
| **Parameter** | **Hazard ratio (95% CI)** | **P value** | **Adjusted hazard ratio (95% CI)** | **Adjusted P value** |
| Age\* | 0.93 (0.9 to 0.97) | <0.001 | 0.95 (0.92 to 0.98) | 0.004 |
| Baseline temperature | 1.84 (1.64 to 2.07) | <0.001 | 1.77 (1.57 to 2) | <0.001 |
| Diagnosis vs. other |  |  |  |  |
| Cardiovascular | 1.67 (0.72 to 3.86) | 0.23 | 1.65 (0.67 to 4.04) | 0.28 |
| Gastrointestinal | 2.14 (0.94 to 4.85) | 0.07 | 2.22 (0.93 to 5.32) | 0.07 |
| Musculoskeletal | 0.78 (0.2 to 3.05) | 0.72 | 0.69 (0.18 to 2.7) | 0.60 |
| Neurological | 1.58 (0.39 to 6.43) | 0.52 | 1.44 (0.41 to 5.03) | 0.57 |
| Respiratory | 2.4 (1.09 to 5.27) | 0.03 | 2.09 (0.9 to 4.86) | 0.09 |
| Sepsis | 2.57 (1.14 to 5.81) | 0.02 | 1.93 (0.8 to 4.63) | 0.14 |
| Assigned to dexmedetomidine group | 1.41 (1.12 to 1.77) | 0.003 | 1.29 (1.04 to 1.61) | 0.02 |
| Weight† | 1.06 (1.02 to 1.1) | 0.006 | 1.03 (0.99 to 1.06) | 0.10 |
| Site 1 | 0.96 (0.65 to 1.4] | 0.82 | 0.63 (0.44 to 0.92) | 0.02 |
| Site 2 | 1.16 (0.78 to 1.7) | 0.47 | 0.81 (0.56 to 1.17) | 0.26 |
| Site 3 | 1.14 (0.79 to 1.64) | 0.48 | 0.78 (0.54 to 1.12) | 0.18 |
| Presence of suspect/proven severe sepsis‡ | 1.46 (1.14 to 1.88) | 0.003 | 1.14 (0.86 to 1.51) | 0.35 |

\* Hazard ratios for age are reported in 5-year blocks

† Hazard ratios for age reported in 10 kg blocks

‡ Patients with suspected or proven sepsis at randomisation may have been assigned another APACHE III diagnostic code such as pneumonia or a respiratory disorder.

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| **Table S4.** Multivariate analysis for time to temperature ≥39°C | | | | |
| **Parameter** | **Hazard ratio (95% CI)** | **P value** | **Adjusted hazard ratio (95% CI)** | **Adjusted P value** |
| Age\* | 0.92 [0.87 to 0.97] | 0.003 | 0.95 [0.9 to 1] | 0.07 |
| Baseline temperature | 2.32 [1.88 to 2.87] | <0.001 | 2.19 [1.74 to 2.75] | <0.001 |
| Diagnosis vs other |  |  |  |  |
| Cardiovascular | 1.98 [0.47 to 8.44] | 0.36 | 1.66 [0.35 to 7.8] | 0.52 |
| Gastrointestinal | 2.3 [0.55 to 9.64] | 0.25 | 2.39 [0.54 to 10.63] | 0.25 |
| Musculoskeletal | 1.58 [0.23 to 10.91] | 0.64 | 1.73 [0.26 to 11.63] | 0.57 |
| Neurological | 2.9 [0.44 to 19.25] | 0.27 | 2.28 [0.43 to 12.21] | 0.34 |
| Respiratory | 2.67 [0.67 to 10.63] | 0.16 | 2.14 [0.51 to 9.04] | 0.30 |
| Sepsis | 3.27 [0.8 to 13.47] | 0.10 | 2.32 [0.52 to 10.29] | 0.27 |
| Assigned to dexmedetomidine group | 1.62 [1.11 to 2.37] | 0.01 | 1.43 [0.99 to 2.07] | 0.05 |
| Weight† | 1.05 [0.98 to 1.13] | 0.16 | 1.01 [0.95 to 1.07] | 0.81 |
| Site 1 | 0.88 [0.45 to 1.7] | 0.70 | 0.6 [0.3 to 1.17] | 0.13 |
| Site 2 | 1.14 [0.59 to 2.18] | 0.70 | 0.76 [0.39 to 1.48] | 0.42 |
| Site 3 | 1.42 [0.78 to 2.56] | 0.25 | 1.01 [0.52 to 1.95] | 0.99 |
| Presence of suspect/proven severe sepsis‡ | 1.66 [1.08 to 2.55] | 0.02 | 1.15 [0.73 to 1.82] | 0.54 |

\* Hazard ratios for age are reported in 5 year blocks

† Hazard ratios for age reported in 10 kg blocks

‡ Patients with suspected or proven sepsis at randomisation may have been assigned another APACHE III diagnostic code such as pneumonia or a respiratory disorder.

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|  | **Figure S2.** Multivariable sensitivity analyses for mean daily temperature (A) and peak daily temperature (B) by treatment group during the first 5 days post randomisation in the ICU\* |  |
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| \* Error bars show standard error mean and are adjusted for admission diagnosis, baseline temperature, patient age, body weight and the stratifying variables of site and presence or absence of known or suspected sepsis. The number of data points by treatment group is shown on the horizontal axis.  Abbreviations: Dex: Dexmedetomidine; ICU: intensive care unit. | | |

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|  | **Figure S3.** Multivariable sensitivity analyses for mean daily temperature (A) and peak daily temperature (B) by treatment group during the first 5 days post randomisation in the ICU\* excluding those with baseline temperatures <35°C (n = 30 (4.3%)) and >38.3°C ( n = 37(5.3%)). |  |
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| \* Error bars show standard error mean and are adjusted for admission diagnosis, baseline temperature, patient age, body weight and the stratifying variables of site and presence or absence of known or suspected sepsis. The number of data points by treatment group is shown on the horizontal axis.  Abbreviations: Dex: Dexmedetomidine; ICU: intensive care unit. | | |

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| **Table S5.** Sensitivity analysis for time to temperature elevation ≥38.3°C  excluding baseline values <35°C and >38.3°C | | | | | |
| **Parameter** | **ClassVal0** | **HRraw\_95** | **RawP** | **HRadj\_95** | **adjP** |
| Age5 |  | 0.97 [0.93 to 1.02] | 0.23 | 0.97 [0.93 to 1.02] | 0.31 |
| BaseTemp |  | 1.87 [1.44 to 2.43] | <0.001 | 1.84 [1.41 to 2.41] | <0.001 |
| Diag | Cardiovascular | 1.54 [0.54 to 4.4] | 0.42 | 1.64 [0.53 to 5.1] | 0.39 |
| Diag | Gastrointestinal | 2.03 [0.73 to 5.6] | 0.17 | 2.58 [0.86 to 7.73] | 0.09 |
| Diag | Musculoskeletal | 0.65 [0.12 to 3.51] | 0.62 | 0.65 [0.12 to 3.61] | 0.62 |
| Diag | Neurological | 0.71 [0.08 to 6.64] | 0.77 | 0.89 [0.09 to 8.34] | 0.92 |
| Diag | Respiratory | 2.32 [0.88 to 6.16] | 0.09 | 2.71 [0.95 to 7.74] | 0.06 |
| Diag | Sepsis | 2.67 [0.97 to 7.35] | 0.06 | 3.19 [1.07 to 9.55] | 0.04 |
| group | A | 1.42 [1.06 to 1.91] | 0.02 | 1.44 [1.07 to 1.94] | 0.02 |
| sepsis |  | 1.4 [1 to 1.94] | 0.05 | 0.95 [0.65 to 1.41] | 0.81 |
| site\_id | 1 | 1.11 [0.68 to 1.81] | 0.68 | 0.92 [0.56 to 1.5] | 0.73 |
| site\_id | 2 | 0.98 [0.58 to 1.67] | 0.95 | 0.87 [0.51 to 1.47] | 0.59 |
| site\_id | 3 | 1.16 [0.72 to 1.89] | 0.54 | 1.06 [0.64 to 1.74] | 0.83 |
| weight10 |  | 1.05 [0.99 to 1.11] | 0.08 | 1.05 [0.99 to 1.11] | 0.09 |

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| **Table S6.** Sensitivity analysis for time to severe body temperature elevation ≥39°C  excluding baseline values <35°C and >38.3°C | | | | | |
| **Parameter** | **ClassVal0** | **HRraw\_95** | **RawP** | **HRadj\_95** | **adjP** |
| Age5 |  | 0.97 [0.9 to 1.06] | 0.51 | 0.97 [0.89 to 1.05] | 0.44 |
| BaseTemp |  | 2.08 [1.4 to 3.08] | <0.001 | 1.96 [1.3 to 2.96] | <0.001 |
| Diag | Cardiovascular | 1.56 [0.19 to 12.89] | 0.68 | 1.74 [0.18 to 16.55] | 0.63 |
| Diag | Gastrointestinal | 2.21 [0.29 to 17.12] | 0.45 | 3.1 [0.37 to 25.71] | 0.29 |
| Diag | Musculoskeletal | 1.32 [0.09 to 20.22] | 0.84 | 1.77 [0.12 to 26.7] | 0.68 |
| Diag | Respiratory | 3.03 [0.43 to 21.58] | 0.27 | 3.64 [0.5 to 26.56] | 0.20 |
| Diag | Sepsis | 3.77 [0.5 to 28.26] | 0.20 | 5.08 [0.63 to 40.8] | 0.13 |
| group | A | 1.92 [1.1 to 3.33] | 0.02 | 1.89 [1.09 to 3.3] | 0.02 |
| sepsis |  | 1.87 [0.99 to 3.52] | 0.05 | 1.14 [0.57 to 2.27] | 0.71 |
| site\_id | 1 | 1.09 [0.42 to 2.81] | 0.86 | 0.95 [0.36 to 2.54] | 0.93 |
| site\_id | 2 | 1.02 [0.37 to 2.79] | 0.97 | 0.96 [0.34 to 2.71] | 0.94 |
| site\_id | 3 | 1.64 [0.68 to 3.98] | 0.27 | 1.92 [0.69 to 5.35] | 0.21 |
| weight10 |  | 0.98 [0.89 to 1.08] | 0.67 | 0.96 [0.85 to 1.07] | 0.47 |

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| **Table S7.** Exploratory post-hoc multivariable analysis | | | | | | | |
| **Variables** | **Category** | **Model 1\*** | | | **Model 2\*\*** | | |
| Effect | Category | **Mean** | **standard error** | **Pvalue** | **Mean** | **Standard error** | **Pvalue** |
| Dexmedetomidine | No | 36.84 | 0.10 | <0.001 |  |  |  |
|  | Yes | 37.03 | 0.10 |  |  |  |  |
| Dexmedetomidine | per 1mcg/kg/hr |  |  |  | 0.3 | 0.08 | <0.0002 |
| Age |  | -0.01 | 0.00 | <0.001 | -0.01 | 0.00 | <0.001 |
| Baseline Temp |  | 0.21 | 0.02 |  | 0.20 | 0.02 |  |
| Diagnosis | Cardiovascular | 37.05 | 0.10 | 0.13 | 37.02 | 0.10 | 0.12 |
|  | Gastrointestinal | 37.05 | 0.10 |  | 37.03 | 0.10 |  |
|  | Haematological | 36.79 | 0.22 |  | 36.74 | 0.22 |  |
|  | Metabolic | 37.10 | 0.28 |  | 37.05 | 0.28 |  |
|  | Musculoskeletal | 36.74 | 0.15 |  | 36.72 | 0.15 |  |
|  | Neurological | 36.85 | 0.18 |  | 36.85 | 0.18 |  |
|  | Renal | 37.03 | 0.24 |  | 37.02 | 0.23 |  |
|  | Respiratory | 36.98 | 0.09 |  | 36.96 | 0.09 |  |
|  | Sepsis | 37.11 | 0.10 |  | 37.09 | 0.10 |  |
|  | Trauma | 36.79 | 0.21 |  | 36.77 | 0.21 |  |
|  | other | 36.84 | 0.22 |  | 36.83 | 0.22 |  |
| Daily Ventilation | No | 36.84 | 0.10 | <0.001 | 36.83 | 0.10 | <0.001 |
|  | Yes | 37.04 | 0.10 |  | 37.00 | 0.10 |  |
| Neuromuscular | No | 36.95 | 0.10 | 0.57 | 36.93 | 0.10 | 0.51 |
| Blockade | Yes | 36.93 | 0.10 |  | 36.90 | 0.10 |  |
| Neuroleptics | No | 36.92 | 0.10 | 0.42 | 36.90 | 0.10 | 0.54 |
|  | Yes | 36.96 | 0.11 |  | 36.93 | 0.10 |  |
| Paracetamol | No | 36.80 | 0.10 | <0.001 | 36.78 | 0.10 | <0.001 |
|  | Yes | 37.07 | 0.10 |  | 37.05 | 0.10 |  |
| Positive | No | 36.86 | 0.10 | 0.002 | 36.84 | 0.10 | 0.002 |
| Blood culture | Yes | 37.02 | 0.11 |  | 36.99 | 0.11 |  |
| Weight>100 kg | No | 36.87 | 0.10 | 0.01 | 36.86 | 0.10 | 0.02 |
|  | Yes | 37.01 | 0.10 | 0.01 | 36.97 | 0.10 | 0.02 |
| Active mobilisation | No | 37.01 | 0.10 | <0.001 | 36.98 | 0.10 | 0.002 |
|  | Yes | 36.87 | 0.10 |  | 36.85 | 0.10 | 0.002 |
| Day | 0 | 36.79 | 0.10 | <0.001 | 36.82 | 0.10 | <0.001 |
|  | 1 | 37.04 | 0.10 |  | 37.02 | 0.10 |  |
|  | 2 | 36.92 | 0.10 |  | 36.89 | 0.10 |  |
|  | 3 | 36.92 | 0.10 |  | 36.88 | 0.10 |  |
|  | 4 | 36.98 | 0.10 |  | 36.94 | 0.10 |  |
|  | 5 | 36.97 | 0.10 |  | 36.94 | 0.10 |  |
| Diazepam | No | 37.23 | 0.06 | <0.001 | 37.20 | 0.06 | <0.001 |
|  | Yes | 36.65 | 0.17 |  | 36.63 | 0.17 |  |
| Propofol | No | 36.84 | 0.10 | <0.001 | 36.83 | 0.10 | <0.001 |
|  | Yes | 37.04 | 0.10 |  | 37.01 | 0.10 |  |
| Renal replacement | No | 37.07 | 0.10 | <0.001 | 37.05 | 0.10 | <0.001 |
| therapy | Yes | 36.81 | 0.10 |  | 36.79 | 0.10 |  |

**\*** Daily dexmedetomidine usage modelled as a binomial variable (yes vs no)

\*\* Daily dexmedetomidine usage modelled as a continuous variable

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| Table S8: Outcomes, co-interventions, and treatments of particular relevance to patients with elevated body temperature | | | | | |
|  | **Dexmedetomidine**  **(n=351)** | **Usual Care**  **(n=352)** | **Estimate\***  **(95% CI)** | | **P value** |
| Outcomes | |  | | **Mean difference**  **(95% CI)** |  |
| Mean daily temperature, °C | 36.84  (36.78 –36.90) | 36.78  (36.72 –36.84) | | 0.06°C  (-0.03 to 0.15°C) | P=0.16 |
| Highest daily temperature mean, °C | 37.41  (37.34 – 37.48) | 37.29  (37.22 – 37.36) | | 0.12°C  (0.03 to 0.22°C) | P=0.012 |
|  |  |  | | **Odds ratio (95% CI)** |  |
| Highest temperature in the first five days in ICU ≥38.3°C – no. (%) | 152 (43.3%) | 115 (32.7%) | | 1.57  (1.16 – 2.14) | P=0.004 |
| Highest temperature in the first five days in ICU ≥39°C – no. (%) | 68 (19.4%) | 44 (12.5%) | | 1.68  (1.11 – 2.54) | P=0.013 |
| Co-interventions and treatments relevant  to patients with elevated body temperature | | | | **Difference in medians**  **(95% CI)** | **P value** |
| Total dose paracetamol – gm; median (IQR) | 5 [0-12] | 4 [0-12] | | 1gm  (-0.9 to 2.9gm) | P=0.57 |
| Daily dose paracetamol – gm | 1 [0-2.8] | 1 [0-3] | | 0gm  (-0.4 to 0.4gm) | P=0.54 |
| Days receiving intravenous antimicrobials in ICU – median (IQR) | 5 [3-6] | 5 [3-6] | | 0 (-0.7 to 0.7) | P=0.68 |
| Sets of blood cultures performed in ICU - median (IQR) | 2 [1-4] | 2 [1-3] | | 0 (-0.3 to 0.3) | P=0.68 |
|  |  |  | | **Odds ratio (95% CI)** |  |
| Patients with positive blood cultures – no.(%) | 59 (16.8%) | 65 (18.5%) | | 0.89 (0.61-1.32) | P=0.56 |
| Received ongoing neuromuscular blockade – no. (%) | 117 (33.3%) | 110 (31.3%) | | 1.10  (0.80 – 1.51) | P=0.56 |
| Received neuroleptic drugs in ICU – no. (%) | 76 (21.7%) | 82 (23.3%) | | 0.91  (0.64-1.30) | P=0.60 |
| Received RRT in ICU – no. (%) | 89 (25.4%) | 74 (21%) | | 1.28  (0.90 – 1.81) | P=0.17 |

\* The widths of the confidence intervals for secondary analyses have not been adjusted for multiplicity and the

intervals should not be used to infer definite differences between the groups

Abbreviations: IQR: Interquartile range; CI: Confidence Interval; RRT: renal replacement therapy.