Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Shehabi Y, Howe BD, Bellomo R, et al. Early sedation with dexmedetomidine in critically ill patients. N Engl J Med 2019;380:2506-17. DOI: 10.1056/NEJMoa1904710

SPICE III Supplementary Appendix

Table of Contents

Trial Personnel

Management committee: Yahya Shehabi (Chair), Yaseen Arabi, Frances Bass, Rinaldo Bellomo, Simon Erickson, Belinda Howe (Senior Project Manager), Suhaini Kadiman, Colin McArthur, Lynnette Murray, Michael Reade, Ian Seppelt, Jukka Takala, Steve A Webb, Matthew P Wise.

Writing committee: Yahya Shehabi, MD, PhD, Belinda Howe, RN, BAppScNur, MPH, Rinaldo Bellomo, MD, PhD, Yaseen M Arabi, MD, Michael J Bailey, PhD, MSc, BSc(Hons), Frances Bass, BN, GCCC, Suhaini Kadiman, MD, Colin McArthur MBChB, FANZCA, FCICM, Lynnette Murray BAppSci, FAIMS, Michael Reade, MBBS, MPH, PhD, Ian Seppelt, MBBS, BScMed, Jukka Takala, MD, PhD, Steve A Webb, MD, PhD, Matthew P Wise, MD, D.Phil, for the SPICE III investigators, and the Australian and New Zealand Intensive Care Society Clinical Trials Group.

Affiliations of the writing committee: Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne, (MB, RB, BH, CM, LM, SAW); Monash University, School of Clinical Sciences, Melbourne (YS), Monash Health, Melbourne (YS); University of New South Wales, Clinical School of Medicine, Sydney (YS); King Saud Bin Abdulaziz University for Health Sciences and King Abdullah International Medical Research Center, Riyadh, Kingdom of Saudi Arabia (YA); King Abdulaziz Medical City, Riyadh, Kingdom of Saudi Arabia (YA); Royal North Shore Hospital, Sydney (FB); The George Institute for Global Health (FB); Austin Health, Melbourne (RB); National Heart Institute, Kuala Lumpur, Malaysia (SK); Auckland City Hospital, Auckland, New Zealand (CM); University of Queensland, Brisbane (MR); Royal Brisbane & Women's Hospital, Brisbane (MR); Australian Defence Force, Brisbane (MR); Sydney Medical School – Nepean, University of Sydney, Sydney (IS); Dept of Clinical Medicine, Macquarie University, (IS); Department of Intensive Care Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland (JT); University of Bern, Bern, Switzerland (JT); St John of God Subiaco, Subiaco (SAW); University Hospital of Wales, Cardiff, United Kingdom (MPW); (all in Australia unless specified).

Independent Data Safety Monitoring Committee (DSMC): Derek Angus (Chair), Chung-Chou H Chang, Jeremy Kahn all of the University of Pittsburgh, Pennsylvania, USA; Damon Scales of the Department of Critical Care Medicine and Sunnybrook Research Institute, Toronto, Ontario, Canada. The independent DSMC oversaw and reviewed all serious adverse

events and received study data at predetermined intervals and as necessary. The DSMC Charter was approved by the DSMC and the study Management Committee, with explicit stopping, reporting and communication rules.

One blinded interim analysis was planned and performed for the purpose of efficacy and safety after 50% (n=2000) of enrolled patients had their survival status at 90-days collected, using a symmetric O'Brien–Fleming design with a two-sided P value of 0.005. This interim analysis was conducted by the trial statistician (M Bailey), who remained blinded to treatment allocation. As the error spending (critical value $|Zk| \geq 1.967$ rather than 1.96) had a negligible effect on expenditure of error, and the primary outcome was analysed with a type I error equal to 0.05.

Study coordinating centre: The Australian and New Zealand Intensive Care Research Centre (ANZIC-RC), School of Public Health and Preventive Medicine, Monash University, Melbourne. Michael J Bailey, Belinda D. Howe, Lynette Murray, Vanessa Singh.

Acknowledgment

We thank Professor Andrew Forbes and Dr Eldho Paul for independent confirmation of statistical analysis and Alisa Higgins for verification of data.

Site investigators (alphabetically by institution and all in Australia unless specified as New Zealand [NZ], Ireland [IR], Italy [IT], Malaysia [MY], Saudi Arabia [SA], Switzerland [CH] or United Kingdom [UK]):

Albury Base Hospital, Albury, NSW, C. Mashonganyika, H. McKee, A. Tonks; Altnagelvin Area Hospital, Londonderry, UK, A. Donnelly, N. Hemmings, S. O'Kane; Auckland City Hospital CVICU, Auckland, NZ, A. Blakemore, M. Butler, K. Cowdrey, J. Dalton, E. Gilder, S. Long, L. McCarthy, S. McGuinness, R. Parke; Auckland City Hospital DCCM, Auckland, NZ, Y. Chen, C. McArthur, R. McConnochie, L. Newby; Austin Health, Melbourne, VIC, R. Bellomo, G. Eastwood, L. Peck, H. Young; Bendigo Hospital, Bendigo, VIC, C. Boschert, J. Edington, J. Fletcher, J. Smith; Blacktown Hospital, Sydney, NSW, K. Nand, A. Raza, T. Sara; Bristol Royal Infirmary, Bristol, UK, J. Bennett-Britton, J. Bewley, V. Bodenham, L. Cole, K. Driver, L. Grimmer, L. Howie, C. Searles, K. Sweet, D. Webster; Central Gippsland Health, Sale, VIC, A. van Berkel, H. Connor, J. Dennett, M. van Der Graaff; Christchurch Hospital, Christchurch, NZ, S. Henderson, J. Mehrtens, K. Miller, E. Minto, A. Morris, S. Noble, K. Parker; 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; Dorset County Hospital, Dorchester, UK, P. Ashcroft, D. Chambler, S. Dukes, A. Harris, S. Horton, S. Sharpe, P. Williams, S. Williams; Dunedin Hospital, Dunedin, NZ, M. Bailey, E. Blazquez, D. France, R. Hutchison, A. O'Connor; Gold Coast University Hospital, Gold Coast, QLD, G. Comadira, M. Gough, M. Tallott; Gosford Hospital, Gosford, NSW, M. Bastick, R. Cameron, S. Donovan, K. Ellis, A. Gaur, R. Gregory, J. Naumoff, E. Turner, M. White; Hornsby Ku-Ring-Gai Hospital, Sydney, NSW, KFJ. Au, J. Fratzia, S. Treloar; Hospital Pulau Pinang, Pulau Pinang, MY, CH. Lim, Maseeda.Y, AP. Tan, CL. Tang, CY. Yong; Inselspital Bern University Hospital, Bern, CH, M. Akaltan, S. Berger, D. Blaser, L. Fazlija, ML. Jong, M. Lensch, R. Ludwig, T. Merz, K. Nettelbeck, M. Roth, M. Schafer, J. Takala, A. Wehr, D. Zacharias; Institut Jantung Negara, Kuala Lumpur, MY, R. Amran, HN. Ashraf, N. Azmi, N. Basri, H. Burhanuddin, Y. Hadinata, A. Hamdan, S. Kadiman, AIYM. Rashid, IN. Sabran, S. Sulaiman, I. N. Zabidi; King Abdulaziz Medical City, King Saud Bin Abdulaziz University for Health Sciences and King Abdullah International Medical Research Center, Riyadh, SA, A. Al-Dawood, M. Aljuaid, H. Al Anizi, A. AlSaeedi, Y. Arabi, M. Dbsawy, A. Deeb, M. Hegazy, M. Ibrahim, Kings College Hospital, London, UK, E. Clarey, E. Corcoran, C. Finney, C. Harris, P. Hopkins, H. Noble, J. Smith, L. Thompson, T. Williams; King Saud Medical City, Riyadh, KSA, LA. Dumlao, R. Bassam, MA. Hassan, N. Naseem, MH. Al-

Kurdi, AM. Al-Harthy; Knox Private Hospital, Melbourne, VIC, S. Bernard, L. Sebafundi, C. Serban; Kuala Lumpar General Hospital, Kuala Lumpur, MY, SK. Lim, N. Mazidah, N. Saidin, N. Sjamsuddin, ITA. Tan, N. Zabidi; Launceston General Hospital and Clifford Craig Medical Research Trust, Launceston, TAS, M. Brain, S. Mineall; Lyell McEwin Hospital, Adelaide, SA, M. Kanhere, N. Soar; Melaka General Hospital, Melaka, MY, N. Abd Kadir, NH. Abdullah, R. Awang, Z. Emperan, NS. Husin, NI. Ismail, SZ. Ismail, FNA. Mohd Khadzali, MF. Norddin; Middlemore Hospital, Auckland, NZ, J. Aguila, C. Bold, B. Clatworthy, A. Dias, C. Hogan, A. Kazemi, V. Lai, R. Song, A. Williams; Monash Medical Centre, Melbourne, VIC, D. Bhatia, L. Bulfin, S. Elliot, P. Galt, K. Lavrans, P. Ritchie, A. Wang; Nepean Hospital, Sydney, NSW, R. Gresham, J. Lowrey, K. Masters, P. Palejs, I. Seppelt, F. Symonds, L. Weisbrodt, C. Whitehead; Newcastle upon Tyne Hospitals (Freeman Hospital and Royal Victoria Infirmary), UK, M. Babio-Galan, V. Calder, I. Clement, A. Harrison, I. McCullagh, C. Scott, L. Thompson; North Shore Hospital, Auckland, NZ, R. Bevan, S. Caniba, D. Hacking, L. Maher; IRCCS San Raffaele Scientific Institute, Milan, IT, ML. Azzolini, P. Beccaria, S. Colombo, G. Landoni, C. Leggieri, C. Luca, D. Mamo, E. Moizo, G. Monti, M. Mucci, A. Zangrillo; Prince of Wales, Sydney, NSW, M. Albania, S. Arora, Y. Shi; Prince Sultan Military Medical City, Riyadh, SA, A. Abudayah, G. Almekhlafi, E. Al Amodi, S. Al Samarrai, M. Badawi, R. Cubio Caba, O. Elffaki, Y. Mandourah, J. Valerio; Princess Alexandra Hospital, Brisbane, QLD, C. Joyce, J. Meyer, E. Saylor, B. Venkatesh, E. Venz, J. Walsham, K. Wetzig; Princess Royal University Hospital, London, UK, E. Clarey, C. Harris, P. Hopkins, H. Noble, L. Thompson, T. Williams; Queen Elizabeth Hospital, MY, TM. Khoo, JES. Liew, AN. Sakthi, A. Zulkurnain; Queen Elizabeth Hospital Birmingham, Birmingham, UK, A. Bamford, C. Bergin, R. Carrera, L. Cooper, L. Despy, K. Ellis, S. Harkett, L. Mee, E. Reeves, C. Snelson, E. Spruce; Queen Elizabeth Hospital Kings Lynn, UK, G. Cooper, R. Hodgson, D. Pearson, M. Rosbergen; Raja Perempuan Zainab II Hospital, Kota Bharu, MY, MN. Ali, NI. Bahar, A. Ismail, WNW. Ismail, NM. Samat, NSM. Piah, R. Abd Rahman; Redcliffe Hospital, Brisbane, QLD, M. Duroux, M. Ratcliffe, T. Warhurst; Rotorua Hospital, Rotorua, NZ, U. Buehner, E. Williams; Royal Berkshire Hospital, Reading, UK, N. Jacques, L. Keating, S. Macgill, KL. Tamang, N. Tolan, A. Walden; Royal Bournemouth Hospital, Bournemouth, UK, R. Bower, J. Cranshaw, K. Molloy, S. Pitts; Royal Brisbane and Women's Hospital, Brisbane, QLD, J. Butler, R. Dunlop, C. Fourie, P. Jarrett, M. Lassig-Smith, A. Livermore, S. O'Donoghue, M. Reade, T. Starr, J. Stuart; Royal Darwin Hospital, Darwin, NT, L. Campbell, M. Phillips, D. Stephens, J. Thomas; Royal Hobart Hospital, Hobart, TAS, D. Cooper, R. McAllister; Royal Infirmary of

Edinburgh, Scotland, UK, G. Andrew, L. Barclay, H. Dawson, DM. Griffith, D. Hope, G. Wojcik, C. McCulloch, R. Paterson; Royal Liverpool Hospital, Liverpool, UK, L. Ascough, C. Paisley, J. Patrick-Heselton, D. Shaw, V. Waugh, K. Williams, I. Welters; Royal Melbourne Hospital, Melbourne, VIC, D. Barge, A. Jordan, C. MacIsaac, T. Rechnitzer; Royal North Shore Hospital, Sydney, NSW, F. Bass, J. Gatward, N. Hammond, P. Janin, A. O'Connor, W. Stedman, E. Yarad; Sarawak General Hospital, Sarawak, MY, NA. Razak, N. Dzulkipli, SL. Jong, K. Asen, WL. Voon, S. Liew; St George's Hospital London, UK, J. Ball, V. Barnes, C. Dalton, S. Farnell-Ward, H. Farrah, K. Maher, J. Mellinghoff, C. Ryan, P. Shirley; St James University Hospital, Dublin, IR, L. Conlon, A. Glover, I. Martin-Loeches, E. O'Toole; St John of God Hospital Subiaco, Subiaco, WA, J. Ewan, J. Ferrier, E. Litton, SA. Webb; St Thomas Hospital, London, UK, , W. Berry, U. Blanco Alonso, A. Bociek, S. Campos, S. Jawara, F. Hanks, A. Kelly, K. Lei, C. McKenzie, M. Ostermann, R. Wan, St Vincent's Hospital, Sydney, NSW, S. Al-Soufi, S. Leow, K. McCann, C. Reynolds; St Vincent's University Hospital, Dublin, IR, K. Brickell, C. Fahey, L. Hays, N. Hyde, A. Nichol, D. Ryan; Sunshine Coast University Hospital and Nambour Hospital, Sunshine Coast, QLD, J. Brailsford, A. Buckley, L. Forbes, T. Maguire, J. Moore, L. Murray; The Northern Hospital, Melbourne, VIC, A. Ghosh, M. Park, S. Said; Toowoomba Hospital, Toowoomba, QLD, J. Smith, A. Visser; Universiti Sains Malaysia Hospital, MY, HZ. Abidin, S. Ali, MH. Hassan, SC. Omar, WFW. Shukeri; University College Hospital London, UK, D. Brealey, G. Bercades, E. Blackburn, N. Macallum, A. Macklin, JH. Ryu, K. Tam, D. Smyth; University Hospital of Coventry and Warwick, Coventry, UK, A. Arif, C. Bassford, C. Morgan, C. Swann, G. Ward, L. Wild; University Hospital Geelong, Geelong, VIC, A. Bone, T. Elderkin, D. Green, D. Sach, T. Salerno, N. Simpson; University Hospital of North Tees, Stockton-on-Tees, UK, F. Brohi, M. Clark, L. Williams; University Hospital of Wales, Cardiff, UK, J. Brooks, E. Cocks, J. Cole, J. Curtin, R. Davies, H. Hill, M. Morgan, N. Palmer, C. Whitton, M. Wise; University Malaya Medical Center, MY, P. Baskaran, MS. Hasan, LY. Tham; Wellington Regional Hospital, Wellington, NZ, R. Sol Cruz, D. Dinsdale, S. Edney, C. Firkin, F. FitzJohn, 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, P. Young; Western General Hospital Scotland, Edinburgh, UK, H. Dawson, DM. Griffith, R. Paterson; Westmead Hospital, Sydney, NSW, P. Clark, J. Kong, J. Ho, V. Nayyar, C. Skelly.

Funding Bodies and Endorsement

SPICE III was funded by the National Health and Medical Research Council of Australia (project grant no. 1043938), the Health Research Council of New Zealand (project grant no. 14/115) and the Institut Jantung Negara Foundation, Kuala Lumpur, Malaysia.

SPICE III was endorsed by the Australian and New Zealand Intensive Care Society Clinical Trials Group, the Irish Critical Care-Clinical Trials Group (ICC-CTG) and the Health Research Board Irish Critical Care-Clinical Trial Network (HRB-ICC-CTN).

Source Data Verification and Monitoring

Data entry and data management was coordinated by the Project Manager and the ANZIC-RC, including programming and data management support.

Several procedures to ensure data quality and protocol standardisation were implemented to minimise bias. These included:

- A start-up meeting for all research coordinators and investigators was held prior to study commencement to ensure consistency in procedures;
- A detailed dictionary defined the data to be collected on the case report form;
- The data management centre performed frequent validation of data, queries and corrections, if errors were found during quality control checks;

Data monitoring: A site initiation teleconference or visit was conducted before site activation. The study was monitored by a representative of the ANZIC-RC. There was at least one routine monitoring visit conducted during the recruitment period and close out was conducted either in person or remotely. Medical records, any other relevant source documents and the site investigator files had to be made available to the ANZIC-RC representative for these monitoring visits during the course of the study and at the completion of the study as needed. Email and telephone communication supplemented site visits. A monitoring report was prepared following each visit and reviewed by the management committee when appropriate. The monitoring report was sent to the principal investigator and research coordinator at the site and filed in the site investigator file.

Table S1 - Inclusion and Exclusion Criteria

Full inclusion criteria
1. Subject has been intubated and is receiving mechanical ventilation
2. The treating clinician expects that the patient will remain intubated until the day after tomorrow (unlikely to be extubated the following day)
3. The patient requires immediate ongoing sedative medication for comfort, safety, and to facilitate the delivery of life support measures
Full exclusion criteria
4. Age less than 18 years
5. Patient is pregnant and/or lactating
6. Has been intubated (excluding time spent intubated within an operating theatre or transport) for greater than 12 hours in an intensive care unit
7. Proven or suspected acute primary brain lesion such as traumatic brain injury, intracranial haemorrhage, stroke, or hypoxic brain injury.
8. Proven or suspected spinal cord injury or other pathology that may result in permanent or prolonged weakness
9. Admission as a consequence of a suspected or proven drug overdose or burns.
10. Administration of ongoing neuromuscular blockade
11. Mean arterial blood (MAP) pressure that is less than 50 mmHg despite adequate resuscitation and vasopressor therapy at time of randomisation
12. 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
13. Known sensitivity to any of the study medications or the constituents of propofol (egg, soya or peanut protein)
14. Acute fulminant hepatic failure
15. Patient has been receiving full time residential nursing care.
16. 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.
17. Patient has an underlying disease that makes survival to 90 days unlikely
18. Patient has been previously enrolled in the SPICE study.

Table S2 - Recruitment by Country

Number of patients recruited in each country (number of sites)	DEX (N=2001)	Usual care (N=1999)
Australia (29)	780	769
New Zealand (8)	502	503
Malaysia (9)	172	177
Saudi Arabia (3)	106	107
Ireland (2)	68	67
Italy (1)	14	13
Switzerland (1)	110	111
United Kingdom (21)	249	252

Table S3 - Baseline Characteristics and Demographics of the Patients

Additional data to Table 1

Characteristics ¥	**DEX (N=1954)**	**Usual care (N=1964)**
Education level, n (%)		
University, College or Higher Degree	287/1621 (17.7)	266/1643 (16.2)
High School Certificate or equivalent	562/1621 (34.7)	609/1643 (37.1)
Did not achieve High School Certificate	772/1621 (47.6)	768/1643 (46.7)
Employment status, n (%)		
Employed, full or part-time	524/1853 (28.3)	529/1866 (28.3)
Unemployed or unable to work	395/1853 (21.3)	418/1866 (22.4)
Retired or full home duties	908/1853 (49.0)	891/1866 (47.7)
Student, full or part time	26/1853 (1.4)	28/1866 (1.5)
Admission source, n (%)		
Emergency department	598/1953 (30.6)	609/1964 (31.0)
Hospital ward	620/1953 (31.7)	592/1964 (30.1)
Transfer from another hospital	145/1953 (7.4)	152/1964 (7.7)
Transfer from another ICU	54/1953 (2.8)	61/1964 (3.1)
Operating room / emergency	361/1953 (18.5)	391/1964 (19.9)
Operating room / elective	175/1953 (9.0)	159/1964 (8.1)
Sedative and analgesic drugs given at randomization, n (%) ¶¶		
Propofol	1479/1855 (79.7)	1523/1857 (82.0)
Midazolam	582/1855 (31.4)	585/1857 (31.5)
Fentanyl	1220/1855 (65.8)	1211/1857 (65.2)

Morphine	257/1855 (13.9)	283/1857 (15.2)
Dexmedetomidine ¥	48/1855 (2.6)	30/1857 (1.6)
Ketamine	128/1855 (6.9)	107/1857 (5.8)

¶¶ Sedatives and analgesics administered could have been given in different combinations.

¥ There were no significant differences in baseline characteristics between the trial groups except pre-randomization dexmedetomidine.

Sensitivity Analysis for 90-day Mortality

Sensitivity analysis for the primary outcome (90-day mortality) was conducted for baseline imbalance and missingness using logistic regression adjusting for sepsis with a robust error structure to account for within-center clustering. Results have been reported as odds ratios (95%CI).

Baseline Imbalance

Using a p-value of 0.05 to indicate imbalance, two baseline variables (weight & dexmedetomidine prior to randomisation) differed significantly between treatment groups (Table 1). To ensure treatment effects were not due to baseline imbalance, these variables were included as covariates in logistic regression modelling.

Missingness

14/3918 (0.4%) patients were missing the primary outcome. Missingness for the primary outcome was conditional on observed covariates and was assumed to be "missing at random". Multiple imputation (10 replications) using fully conditional specification logistic regression was performed based on prognostic baseline and post-baseline variables.

Results

90-day mortality

Approach	Odds Ratio DEX vs Usual	P-value
Baseline Imbalance	0.98 (0.85-1.14)	0.80
Missingness	1.00 (0.87-1.15)	0.99

Table S4 Primary outcome by country:

Country	Dexmedetomidine		usual care		Difference
	N	90 day mortality	N	90 day mortality	(95%CI)
Australia	751	203 [27% (23.8-30.3%)]	750	174 [23.2% (20.1-26.3%)]	3.8(-0.6 to 8.2)
Switzerland	105	24 [22.9% (14.6-31.1%)]	108	26 [24.1% (15.8-32.3%)]	-1.2(-12.6 to 10.2)
Ireland	72	34 [47.2% (35.4-59.1%)]	69	30 [43.5% (31.5-55.5%)]	3.7(-12.7 to 20.2)
Malaysia	171	50 [29.2% (22.3-36.2%)]	176	57 [32.4% (25.3-39.5%)]	-3.1(-12.9 to 6.6)
United Kingdom	237	84 [35.4% (29.2-41.7%)]	240	93 [38.8% (32.4-45.1%)]	-3.3(-12 to 5.4)
New Zealand	499	127 [25.5% (21.5-29.4%)]	496	145 [29.2% (25.1-33.3%)]	-3.8(-9.3 to 1.8)
Saudi Arabia	99	38 [38.4% (28.6-48.2%)]	104	38 [36.5% (27-46%)]	1.8(-11.5 to 15.2)
Italy	14	6 [42.9% (15.4-70.3%)]	13	6 [46.2% (17.4-74.9%)]	-3.3(-40.8 to 34.2)

Table S5 – Cause of Death up to Day 90

Cause of Death to Day 90	DEX (N=566)	Usual care (N=569)
Arrhythmia	17 (3.0%)	14 (2.5%)
Cardiogenic shock	56 (9.9%)	65 (11.4%)
Distributive (septic) shock	224 (39.6%)	201 (35.3%)
Hypovolemic shock	10 (1.8%)	12 (2.1%)
Respiratory	132 (23.3%)	156 (27.4%)
Metabolic	9 (1.6%)	13 (2.3%)
Multi-Organ Failure	40 (7.1%)	46 (8.1%)
Other	78 (13.8%)	62 (10.9%)

Table S6 – Discharge Destination

Discharge destination	DEX N=1445	Usual Care N=1449	Odds Ratio (95%CI)
Home	987 (68.3%)	1002 (69.2%)	
Other acute hospital	229 (15.8%)	206 (14.2%)	1.13 (0.92-1.39)
Rehabilitation hospital	201 (13.9%)	216 (14.9%)	0.95 (0.77-1.17)
Nursing home / long term care facility	28 (1.9%)	25 (1.7%)	1.14 (0.66-1.97)

Statistical Analysis of Tertiary Outcomes

Binomial tertiary outcomes (in-hospital mortality, ICU mortality, delirium incidence, tracheostomy receipt, requirement of physical restraints, unplanned extubation, reintubation, active mobilization, readmission to ICU) have been summarised using the observed proportions of the outcome in each treatment arm, and compared using logistic regression adjusting for sepsis status with results reported as odds ratios (95%CI). To account for the competing risk of death, comparisons between treatment arms for length of stay in ICU and in hospital were performed using sub-distribution hazard regression models, accounting for sepsis and site with results reported as hazard ratios (95%CI) representing the relative discharge probability on a given day between the two treatment arms in subjects who have not yet been discharged. Proportionality of hazards were assessed by fitting an interaction terms between treatment arm and time and were found to be satisfactory for both models. (Hospital: p=0.28 ICU: p=0.85).

Days alive and coma-free at day 28 and duration of ventilation have been reported as medians [interquartile range]. Duration of ventilation has been further stratified by survival status for increased transparency. Discharge destination (home, rehabilitation facility, nursing home and other acute hospital) have been analysed using multinomial logistic regression adjusting for sepsis with results reported as respective proportions (%) with corresponding odds ratios (95%CI) between treatment arms referenced against discharge to home. Cause of death has been reported as proportions (%).

Table S7 - Tertiary and Process Related Outcomes

Outcome	DEX N=1954	Usual Care N=1964	Odds Ratio † 95%CI
Mortality at hospital discharge N (%)	506/1952 (25.9)	513/1962 (26.1)	0.99 (0.86-1.14)
Median hospital LOS d (IQR)	13.5 (7.0-25.9)	13.2 (7.3-26.1)	0.99 (0.92-1.07)*
Mortality at ICU discharge N (%)	410/1952 (21.0)	410/1963 (20.9)	1.01 (0.86-1.18)
Median ICU LOS d (IQR)	6.0 (3.1-11.2)	6.3 (3.2-12.3)	1.00 (0.93-1.07)*
Median duration of ventilation days, (IQR): all	3.0 (1.5-7.1) N=1942	3.3 (1.7-8.0) N=1958	
survivors	2.8 (1.4-6.2) N=1439	3.0 (1.7-6.9) N=1445	
non-survivors	4.4 (1.7-9.5) N=503	5.1 (1.8-11.3) N=514	
Median days coma-free (IQR) ⅂	25 (14-27)	24 (14-26)	
Delirium at any point during stay N (%)⅂	796 (40.7)	835 (42.5)	0.93 (0.82-1.06)
Tracheostomy N (%)⅂	231 (11.8)	266/1963 (13.6)	0.85 (0.71-1.03)
Physical restraints N (%)⅂	490 (25.1)	501/1963 (25.5)	0.98 (0.85-1.13)
Unplanned extubation N (%)⅂	87 (4.5)	70 (3.6)	1.26 (0.91-1.74)
Re-intubation N (%)⅂	285 (14.6)	232/1962 (11.8)	1.27 (1.06-1.53)
Active mobilization N (%)⅂	1110 (56.8)	1125/1963 (57.3)	0.98 (0.86-1.11)
Readmission to ICU N (%)	169/1542 (11.0)	140/1553 (9.0)	1.24 (0.98-1.57)

† Odds ratio for DEX vs usual care.

*Hazard ratios for the probability of discharge from Hospital and ICU, Interquartile Range (IQR). Intensive Care (ICU), Length of stay (LOS). d indicates days. N= number of patients

⅂ During ICU stay up to 28 days which ever came first.

Table S8: Post Randomization Sedative, Analgesic and Adjunct Medications

Medication ¶ ¶	DEX ¶ N=1954	Usual Care ¶ N=1964
Dexmedetomidine		
Patients N (%)	1910 (97.8)	226 (11.5)
Median duration of infusion [IQR] d	2.56 [1.10 to 5.32]	1.26 [0.67 to 3.29]
Propofol		
Patients N (%)	1679 (86.0)	1741 (88.7)
Median duration of infusion [IQR] d	1.95 [0.79 to 4.66]	2.67 [1.36 to 5.70]
Midazolam		
Patients N (%)	455 (23.3)	794 (40.4)
Median duration of infusion [IQR] d	0.50 [0.21 to 1.87]	1.51 [0.67 to 3.17]
Fentanyl		
Patients N (%)	1534 (78.5)	1584 (80.7)
Morphine		
Patients N (%)	580 (29.7)	613 (31.2)
Alfentanil		
Patients N (%)	152 (7.8)	146 (7.4)
Haloperidol		
Patients N (%)	236 (12.1)	277 (14.1)
Neuromuscular blockade (NMB) N (%) *	684 (35.0)	692 (35.3)
NMB for ≥ 2 consecutive days N (%)	265 (13.6)	278 (14.2)
Indication for benzodiazepines in DEX arm **		
Uncontrolled agitation/delirium N (%)	41 (2.1)	-
Concomitant NMB N (%)	102 (5.2)	-
Seizures N (%)	26 (1.3)	-
Palliation N (%)	109 (5.6)	-
Procedural sedation N (%)	138 (7.1)	-

¶ Administered in ICU over study period up to 28 days or ICU discharge. [IQR] denotes Interquartile range

¶¶ Mean daily dose given is presented in [Figure 1 A-D]. Drugs administered could have been given in different combinations.

* Received at least once for reasons other than intubation

** Given for per protocol pre-specified clinical indication in DEX arm. Daily treatments are shown in Figure S4, Panel A.

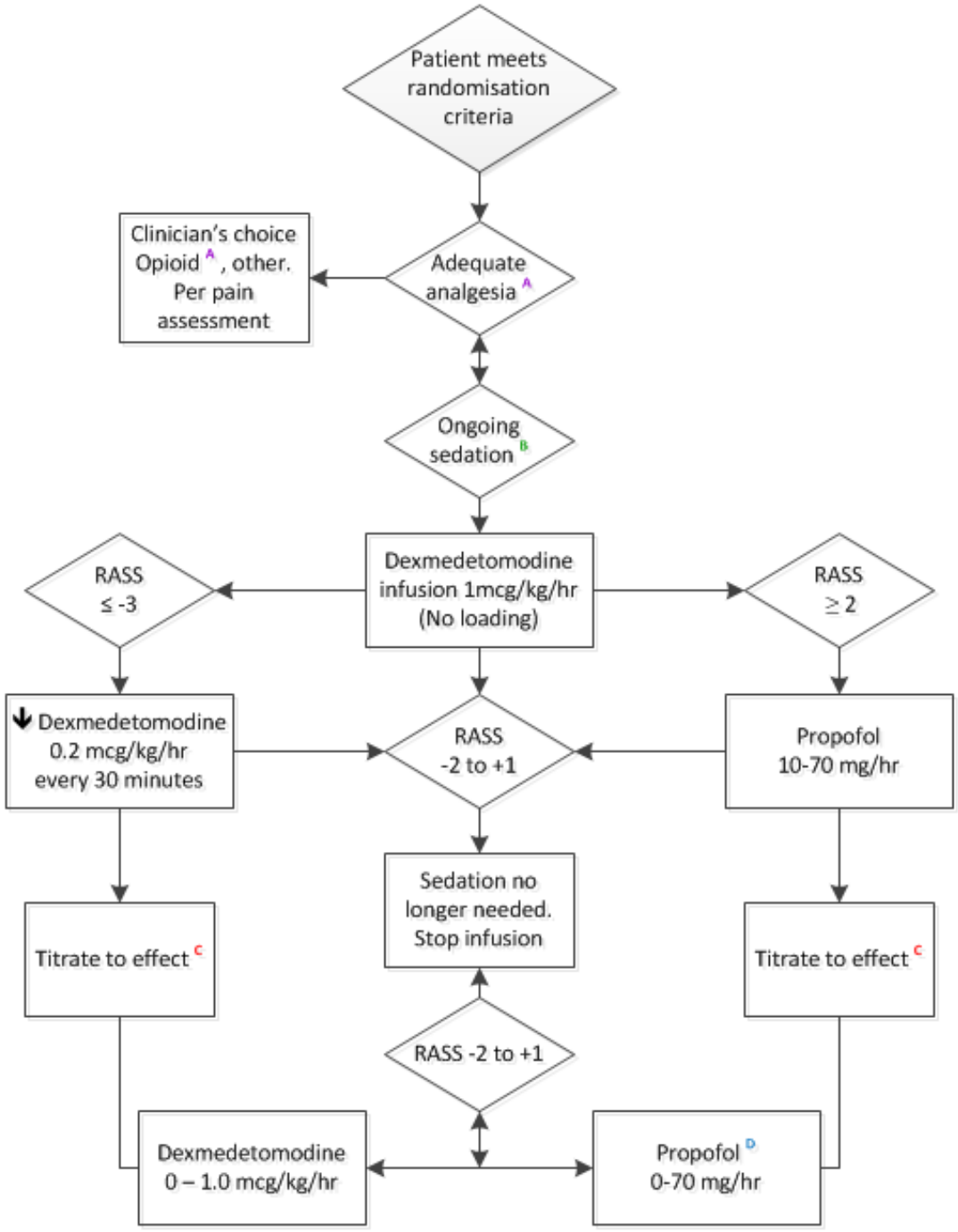
Table S9 –Reported Adverse and Serious Adverse Events[¥]

	DEX (N=1954)	Usual care (N=1964)	P value
One or more AE during study	188 (9.6%)	35 (1.8%)	< 0.0001
One or more SAE during study	52 (2.7%)	7 (0.4%)	< 0.0001
Adverse Events:			
Bradycardia	99 (5.1%)	9 (0.5%)	< 0.0001
Hypotension	52 (2.7%)	10 (0.5%)	< 0.0001
Other AE	44 (2.3%)	16 (0.8%)	< 0.0001
Serious Adverse Events:			
Bradycardia	13 (0.70%)	1 (0.05%)	0.001
Hypotension	10 (0.50%)	1 (0.05%)	0.006
Prolonged sinus pause (Asystole)	14 (0.70%)	2 (0.10%)	0.003
Other SAE	16 (0.82%)	3 (0.15%)	0.003
Uncontrolled agitation during study	44 (2.3%)	77 (3.9%)	0.003
Protocol deviation during study	360(18.4%)	214 (10.9%)	< 0.0001

[¥] Table describes number of patients (%) who experienced each event on one or more occasions. Patients can have multiple AEs/SAES. AEs and SAEs were defined in the protocol. Due to the un-blinded study design, events were reported by site investigators but not systematically collected in both groups.

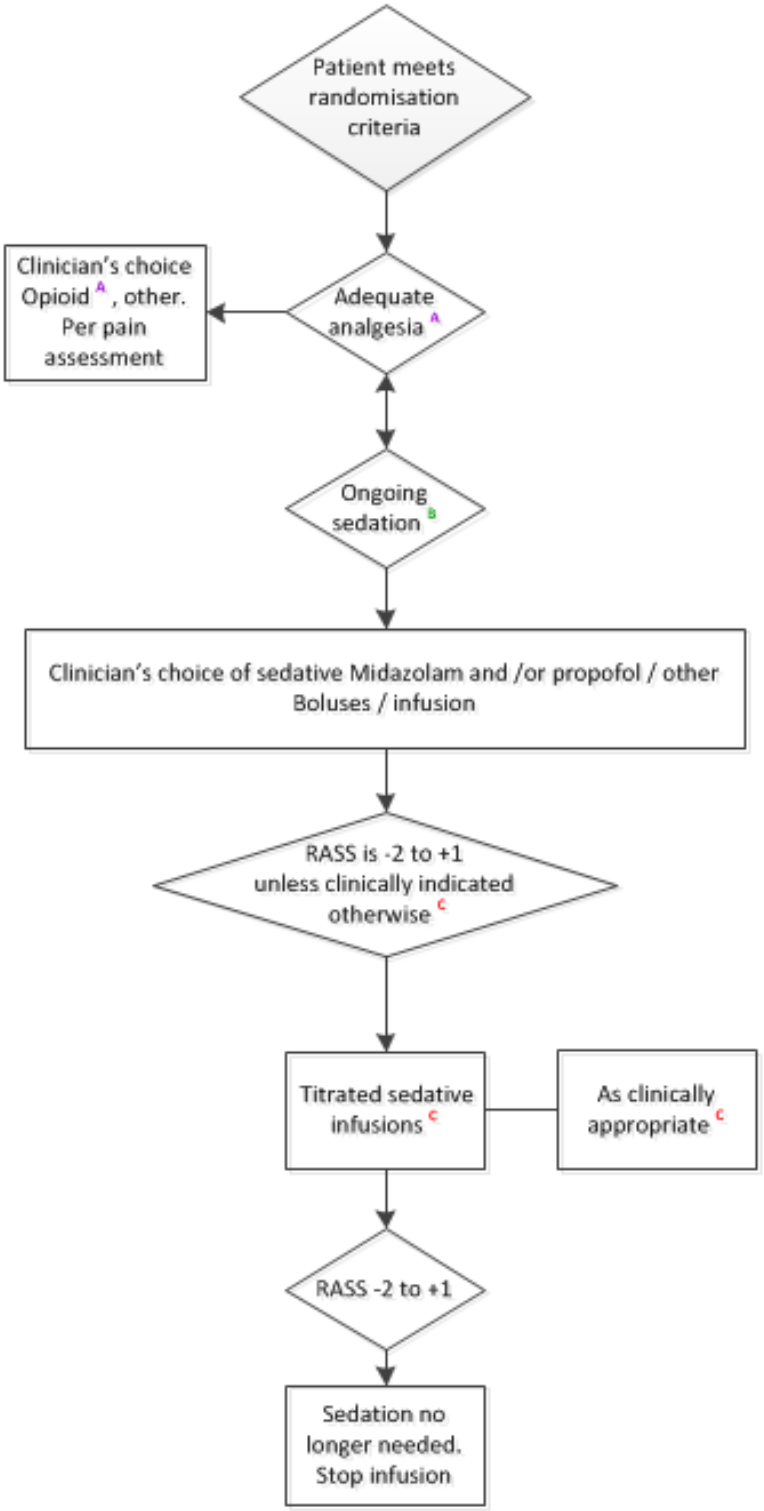
Figure S1 - Study Algorithms

Early Dexmedetomidine Sedation Treatment Algorithm (DEX):



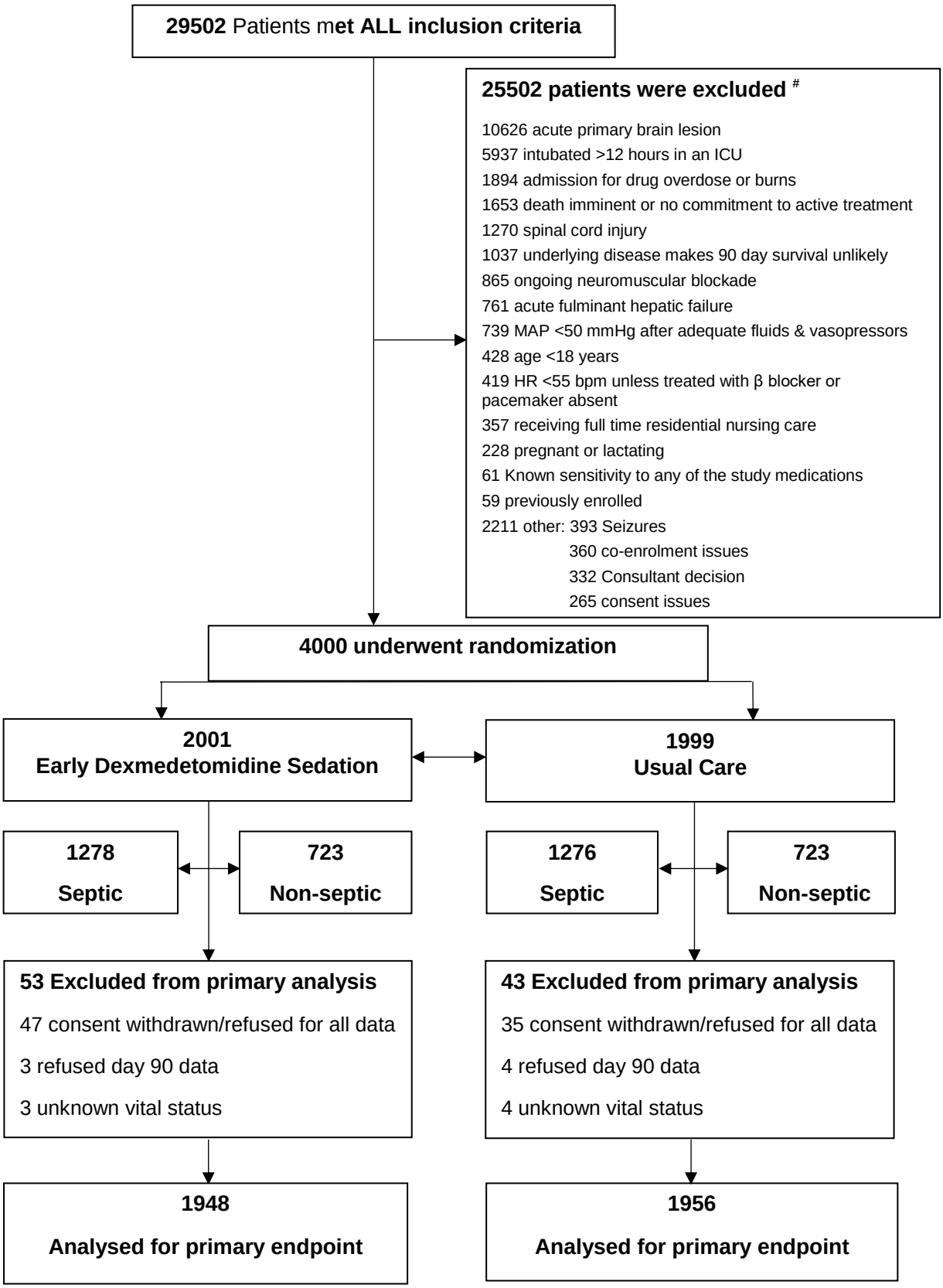
A: Opioids can be given by infusion or boluses and continued as needed throughout study period, the use of remifentanil is not permitted.
B: Benzodiazepines in all forms and injectable clonidine are precluded.
C: Reduce propofol first 20mg / hr every 15 minutes to lowest effective dose required.
D: If RASS ≥ 2 (agitation) continues, propofol can be titrated up to 200 mg/hr.

Usual Care Treatment Algorithm:



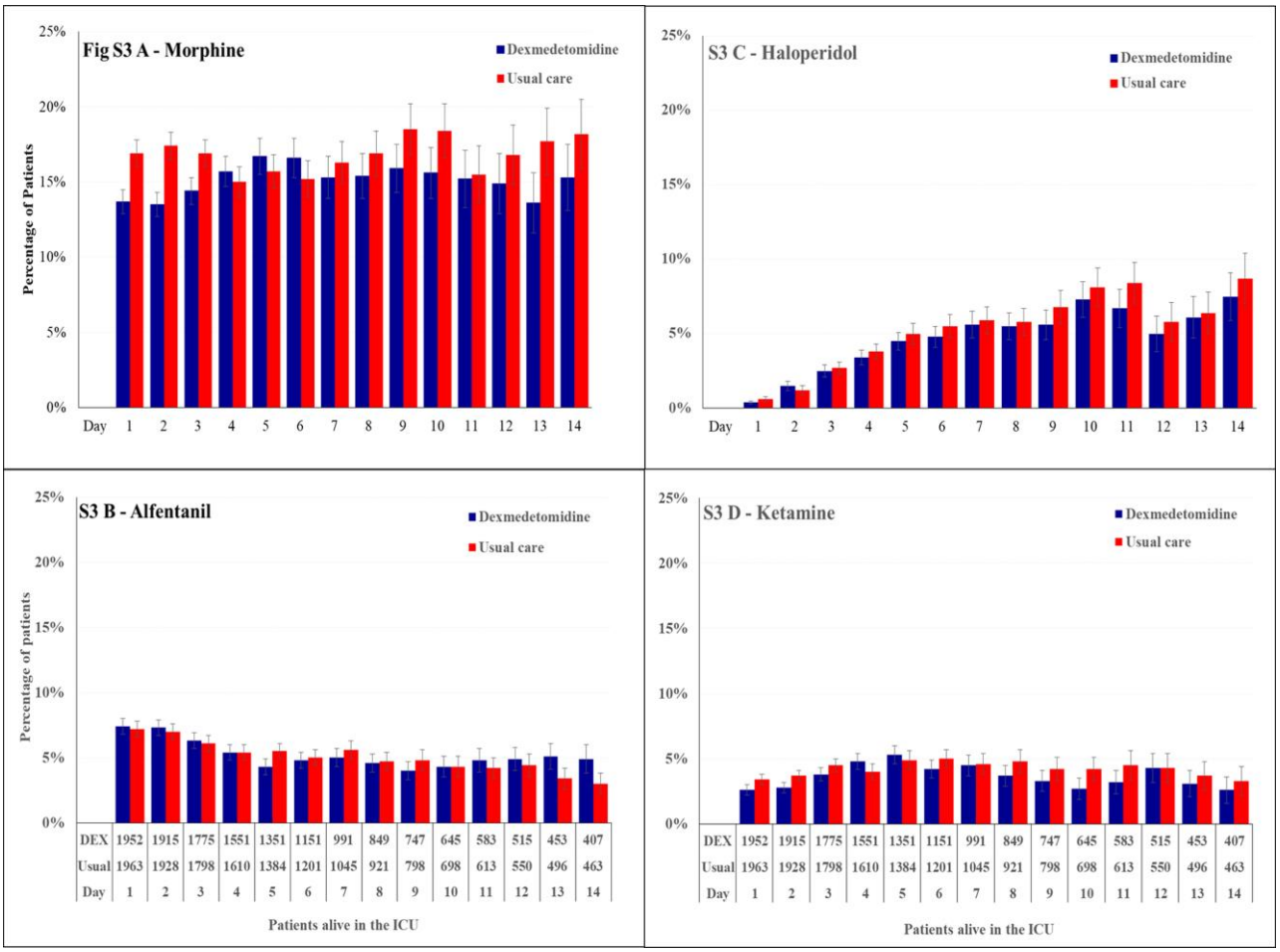
A: Opioids can be given by infusion or boluses and continued as needed throughout study period, the use of remifentanil is not permitted.
B: Dexmedetomidine and injectable clonidine are precluded.
C: RASS -2 to +1 is encouraged. Midazolam and/or propofol / other sedatives are titrated as clinically appropriate.

Figure S2 - Screening, Randomisation and Follow up



Patients can meet more than 1 exclusion criterion

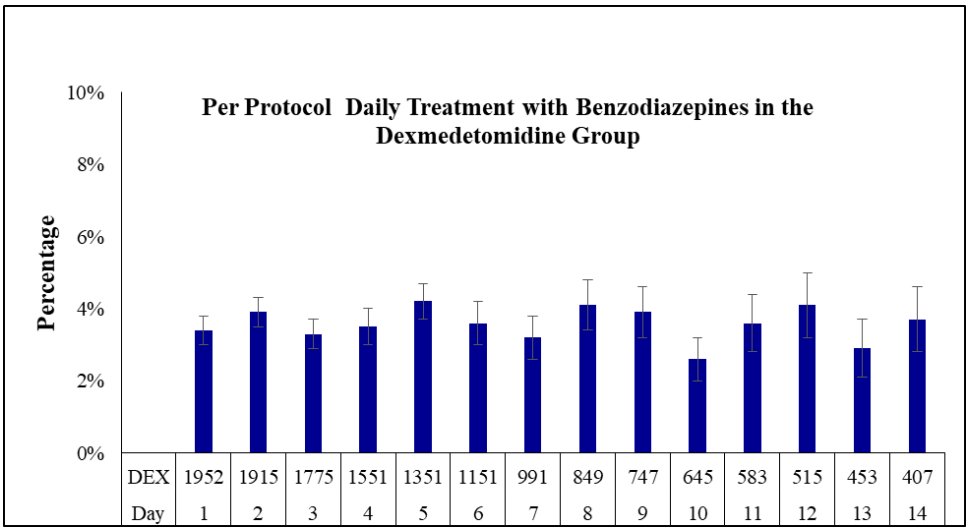
Figure S3: Daily Treatment with Opioids and Adjunct Medications



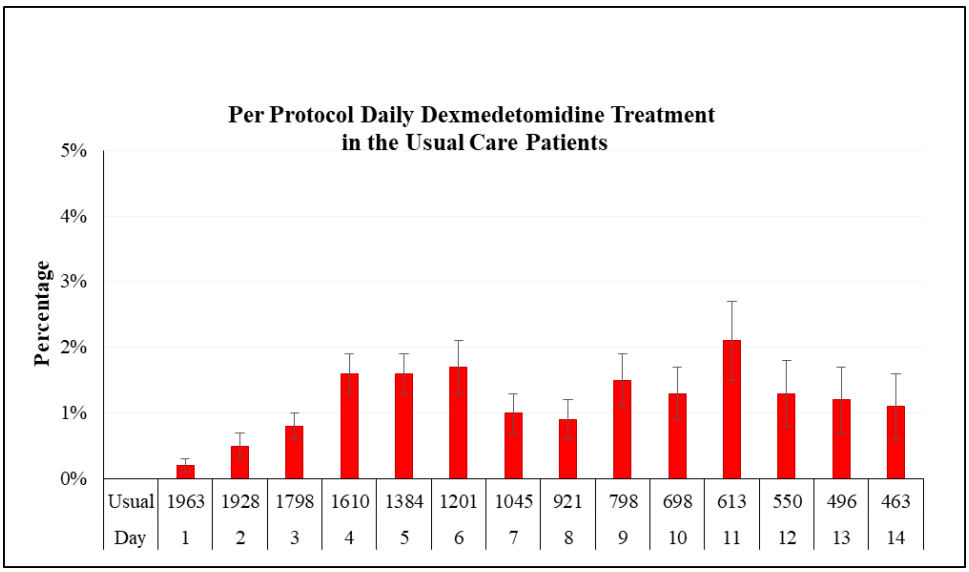
These bar graphs present the daily percentage of patients in each study arm who were treated with morphine (Panel A), alfentanil (Panel B), haloperidol (Panel C) and Ketamine (Panel D).

Figure S4:
Per Protocol Treatment with Benzodiazepines in the (DEX group) and Dexmedetomidine in the (Usual Care group)

Panel A



Panel B



Panel A: The bar graphs depict the daily percentage of patients who were treated with a benzodiazepine in the dexmedetomidine group. Panel B: patients treated with dexmedetomidine in the usual care group according to study protocol and for specific clinical indication.

Cognitive Function and Quality of Life

Sensitivity to Missingness in Survivors

To account for missingness in survivors, multiple imputation (10 replications) was employed under the assumption that missingness was 'missing at random' and conditional on baseline and post-baseline covariates. The Short-IQ code[1] has 16 questions, each with 5 ordinal responses ranging from 1 (much improved) to 5 (much worse). As such, predictive mean matching was employed to generate response for each of the 16 questions with a summary score determined by averaging the 16 responses. Comparison between treatments was performed using linear modelling employing a robust error structure to account for clustering at a site level with results reported as means (95%CI) and differences (95%CI).

The EQ-5D-3L[2] health state scale is a self-reported quality of life measurement on a continuous scale ranging from 0 (poor) to 100 (good). Multiple imputation was performed using fully conditional specification linear regression using prognostic baseline and post-baseline variables. Treatment comparisons were performed using linear modelling accounting for within site clustering with robust errors. Results have been reported as means (95%CI) and differences (95%CI).

Results – sensitivity to missingness for survivors only

Short IQ was missing for 647 (23.3%) survivors while the EQ5D health state scale was missing for 462 (16.6%) of survivors.

Outcome	DEX	Usual	Difference	P-value
Short IQ	3.13 (3.09-3.17)	3.08 (3.03-3.12)	0.05 (0.01-0.09)	0.009
EQ5D-health state scale	67.1 (64.2-69.9)	67.6 (66.8-68.6)	-0.5 (-2.2 to 1.1)	0.54

Truncation due to Death

To account for the competing risk of death, composite outcomes combining death were created for the Short-IQ score and the EQ-5D-3L health state scale. In accordance with Lachin[3], a composite outcome was created by combining survival information with cognitive function and quality of life using the following two rules.

a) All survivors are ranked higher than non-survivors with non-survivor ranking according to time to death with early mortality considered worse than late mortality.
b) Among survivors, higher Short-IQ scores are considered a worse outcome than lower Short-IQ scores, whereas for the EQ-5D-3L health state scale, lower health scores are considered a worse outcome than higher scores.

Composite Short-IQ

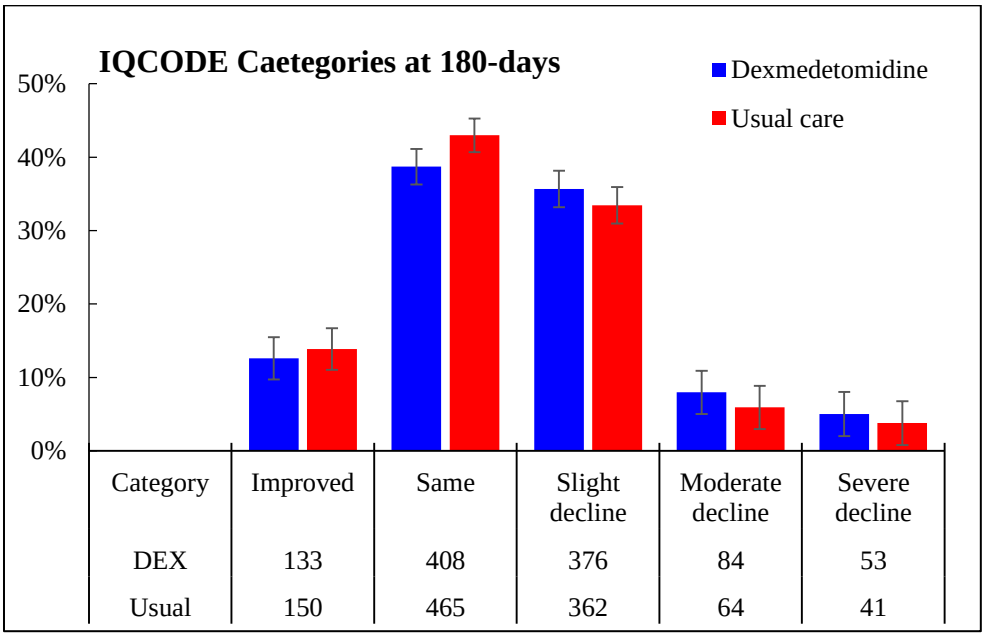
All non-survivors were given a score between 0-180 representing the number of days from randomisation to death. All survivors with missing cognitive function were given a score of 181. As short-IQ values range from 0-5 with a higher score indicating worse cognitive function, all surviving patients with 180 day cognitive function scores were subtracted from 190 such that their scores then ranged from 185 – 189 with a higher composite score indicating better cognitive function. The median composite outcome score was compared between treatment arms using a Wilcoxon rank sum test and reported as a median (interquartile range).

Composite EQ-5D-3L health state scale

All non-survivors were given a score between 0-180 representing the number of days from randomisation to death. All survivors with missing score were given a score of 181 while all survivors with non-missing scores had 181 added to their health state score to create a new composite outcome. The median composite outcome score was compared between treatment arms using a Wilcoxon rank sum test and reported as a median (interquartile range).

Outcome	DEX	Usual	P-value
Composite Short IQ	186.3 (33-187)	186.5 (34-187)	0.10
Composite EQ5D-health state scale	231 (33-261)	231 (34-261)	0.36

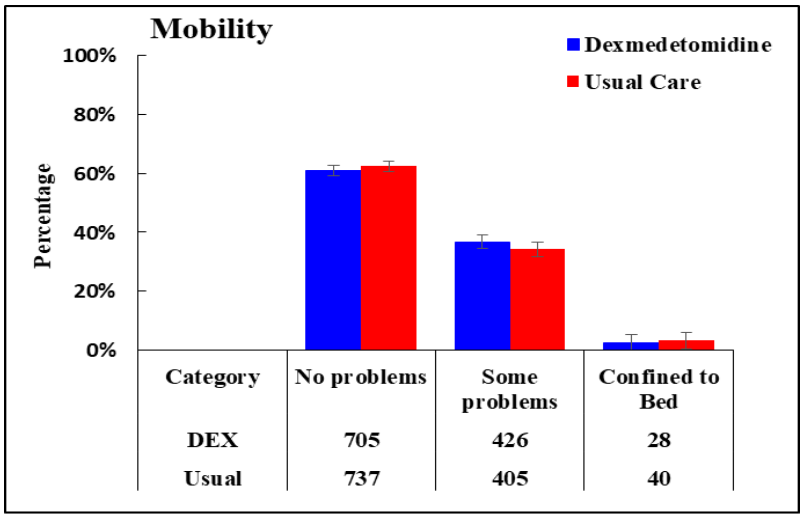
Fig S 5: IQCODE Category Scores

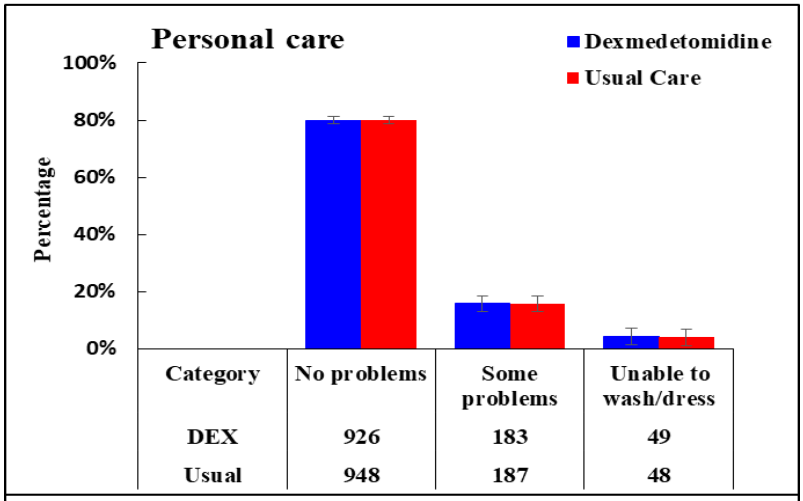


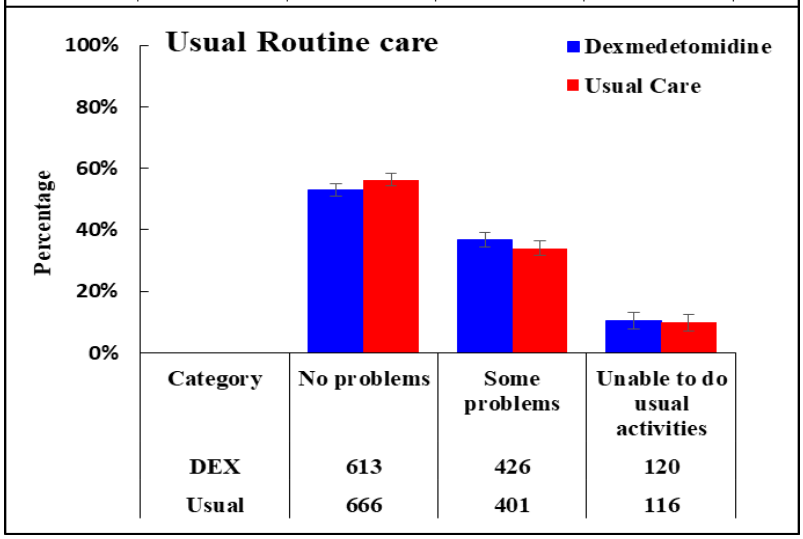
Category	Improved	Same	Slight decline	Moderate decline	Severe decline
DEX	133	408	376	84	53
Usual	150	465	362	64	41

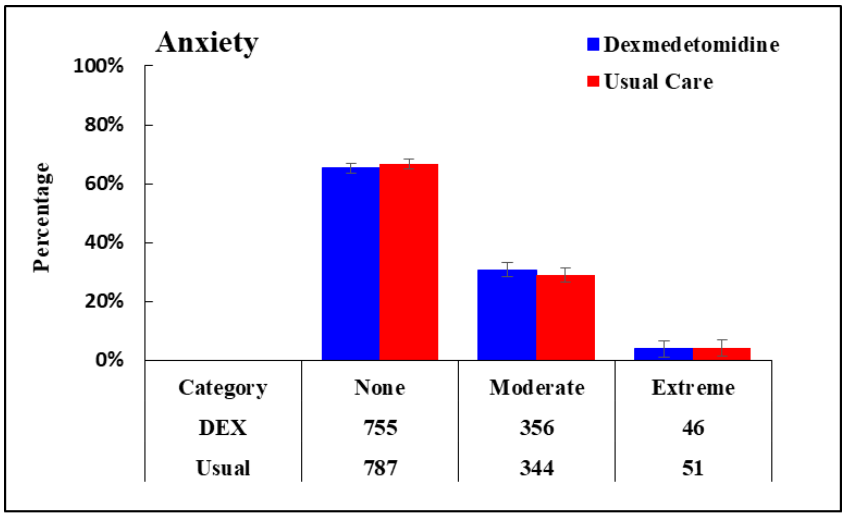
The short IQCODE: The Informant Questionnaire on Cognitive Decline in the Elderly, a measure of cognitive function reported by a significant other relative (the informant) over time on 5 point Likert scale. The bars represent the percentage of patients in each cut-off range of the scale. The average score from 16 questions is on a scale of 1 to 5, a score of less than 3 = improvement, score of 3 indicates no change, score of 3.01 to 3.50 indicates slight decline, score of 3.51 to 4 indicates moderate decline and 4.01 to 5 severe decline. After adjustment for missingness, or in combination with death as a composite outcome, (see above) there was no significant difference between treatment groups. Similarly, when analysed as categories using a chi-square test for equal proportion, there was again no difference between treatment groups (p=0.06).

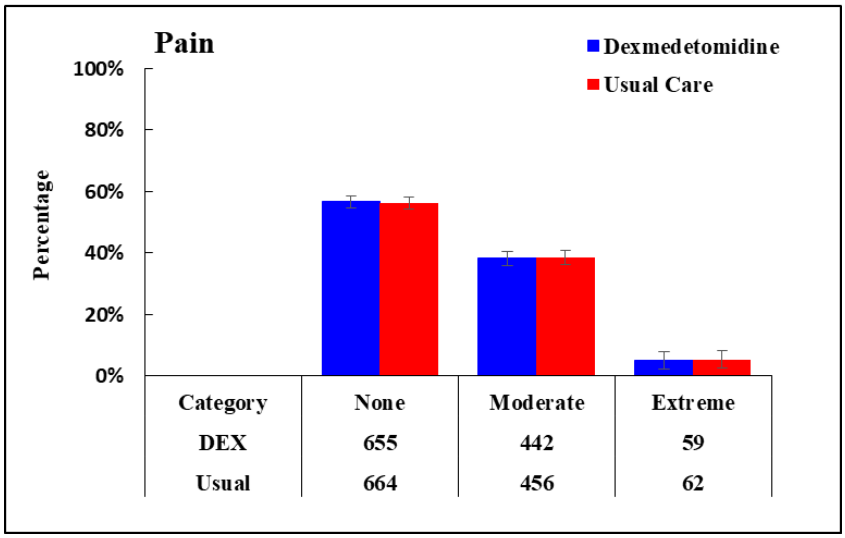
Fig S 6: Health Related Quality Outcome at 180-Days











Euro Quality of Life 5 dimensions descriptive questionnaire is a self-reported Health State Scale from 0-100, lower score indicates worst quality of life. The bar graphs represent the proportion of patients and scores in each of the five dimensions. The majority reported no problems in each the five domains and there was no significant difference between treatment arms.

References:

1. Jorm AF. A short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): development and cross-validation. Psychol Med 1994;24:145-53.
2. Rabin R, Gudex C, Selai C, Herdman M. From translation to version management: a history and review of methods for the cultural adaptation of the EuroQol five-dimensional questionnaire. Value Health 2014;17:70-6.
3. Lachin JM. Worst-rank score analysis with informatively missing observations in clinical trials. Control Clin Trials 1999;20:408-22.