Appendix F: Multivariate risk factors: Pharmacological Risk Factors review

Risk factor: **Benzodiazepines**

Outcome measured incidence of delirium

drug: Midazolam

Study name	*Outcome*	*Sum stats (95%CI)*	*comments:*	*risk factor details:*	*other details:*	*factors adjusted for in multivariate analysis*	
Pandharipande 2006; prospective cohort study in 198 patients. Funding: Grant-other. Setting: Hospital; ICU ward . QUALITY RATING: moderate	multivariate adjusted OR	1.7 (0.9, 3.2)	The risk in the daily transition to delirium associated with every unit dose of midazolam(in loge mg) adminstration in the previous 24h	Midazolam	Age: 55.5 years(38.5 to 72.5) Cognitive impairment: Cognitive impairment deduced from scores; Blessed Dementia Rating score: 0.2 (SD 0.7); range: 0 to 17. Sensory impairment: 58% visual & 16% hearing impairment. Medications: antipsychotics,anticholinergics, opioids, sedatives	age, gender, visual and hearing deficits, history of dementia, depression, severity of illness [modified APACHE II], sepsis, history of neurologic disease (stroke, epilepsy, other CNS), baseline hematocrit, daily glucose concentration, cognitive status at previous 24 h and medications [lorazepam, midazolam, fentanyl, morphine, propofol]	No.events/no. covariates = 118/17 = 7. Number key RFs: 3/3 (age, sensory impairment, dementia). Number of pts with delirium at baseline: delirium (for those taking antipsychotics)66/75; no. pts developing delirium: during ICU stay: 52/63 those taking anticholinergics; 66/75

Risk factor: **Benzodiazepines**

Outcome measured incidence of delirium

drug: Lorazepam

Study name	*Outcome*	*Sum stats (95%CI)*	*comments:*	*risk factor details:*	*other details:*	*factors adjusted for in multivariate analysis*	
Pandharipande 2006; prospective cohort study in 198 patients. Funding: Grant-other. Setting: Hospital; ICU ward . QUALITY RATING: moderate	multivariate adjusted OR	1.2 (1.1, 1.4)	every unit dose of lorazepam (in log e mg) adminstration in the previous 24h	Lorazepam	Age: 55.5 years (38.5 to 72.5) Cognitive impairment: Cognitive impairment deduced from scores; Blessed Dementia Rating score: 0.2 (SD 0.7); range: 0 to 17. Sensory impairment: 58% visual & 16% hearing impairment. Medications: antipsychotics,anticholinergics, opioids, sedatives	age, gender, visual and hearing deficits, history of dementia, depression, severity of illness [modified APACHE II], sepsis, history of neurologic disease (stroke, epilepsy, other CNS), baseline hematocrit, daily glucose concentration, cognitive status at previous 24 h and medications [lorazepam, midazolam, fentanyl, morphine, propofol]	No.events/no. covariates = 118/17 = 7. Number key RFs: 3/3 (age, sensory impairment, dementia). Number of pts with delirium at baseline: delirium (for those taking antipsychotics)66/75; no. pts developing delirium: during ICU stay: 52/63 those taking anticholinergics; 66/75

Appendix F: Multivariate risk factors: Pharmacological Risk Factors review

Risk factor: Benzodiazepines

Outcome measured incidence of delirium

drug: Benzodiazepines

Study name	*Outcome*	*Sum stats (95%CI)*	*comments:*	*risk factor details:*	*other details:*	*factors adjusted for in multivariate analysis*	
Foy 1995; prospective cohort study in 418 patients. Funding: Grant-other. Setting: Hospital; Mixed: Medical/Surgical ward (likely to be mixed surgery). QUALITY RATING: low	multivariate adjusted OR	1 (0.3, 3)	Benzodiazepine usage over previous 5 days (not significant)	Benzodiazepines	Age: 70.2 years(59 to 88) Cognitive impairment: No patients with cognitive impairment; Assessed with MMSE;. Sensory impairment: no details. Medications: Medications at admission-no details for polypharmacy	benzodiazepiones in urine, hypoxia, previous medical diagnosis of CNS & mental disorders, alcohol consumptions >40mg/day, sepsis, admission diagnosis, cerebrovascular accident, benzodizepine use in past 5 days, dehydration, neuroleptics or ricyclics in past 5 days	No.events/no. covariates = 21/12 = 2. Number key RFs: 1/3 (age). Number of pts with delirium at baseline: None; no. pts developing delirium: 21 patients developed delirium (DSM III)

Risk factor: Antipsychotics

Outcome measured duration of delirium

drug: Haloperidol

Study name	*Outcome*	*Sum stats (95%CI)*	*comments:*	*risk factor details:*	*other details:*	*factors adjusted for in multivariate analysis*	
Pisani 2009; prospective cohort study in 304 patients. Funding: Grant-other. Setting: Hospital; ICU ward . QUALITY RATING: low	multivariate adjusted OR	1.35 (1.21, 1.5)		Haloperidol	Age: 75 years (67 to 83) Cognitive impairment: Some patients with cognitive impairment; baseline dementia assessed using IQCODE. Sensory impairment: no details. Medications: benzodiazepine or opiod (81%); medium to high potency ACH (32%), haloperidol (32%), steroid use (52%)	MV: medications (benzodiazepine or opioid use; medium to high potency ACH use; halperidol ause nytime during ICU stay; steroid use anytime during ICU stay), impairment in ADL, depression, dementia, admitting diagnosis of respiratory disease, APACHE II(minus Glasgow Coma Scale), alanine aminotransferase>40 U/l	No.events/no. covariates = 304/10 = 30. Number key RFs: 1/3 (dementia). Number of pts with delirium at baseline: not clear; no. pts developing delirium: 239/304 (79%) developed delirium during ICU stay

Appendix F: Multivariate risk factors: Pharmacological Risk Factors review

Risk factor: **Anticholinergic agents**

Outcome measured incidence of delirium

drug: Diphenhydramine

Study name	*Outcome*	*Sum stats (95%CI)*	*comments:*	*risk factor details:*	*other details:*	*factors adjusted for in multivariate analysis*	
Marcantonio 1994; case control study in 245 patients. Funding: Mixed. Setting: Hospital; Surgical ward (likely to be mixed surgery). QUALITY RATING: low	multivariate adjusted OR	1.8 (0.71, 4.56)		Diphenhydramine	Age: 73 years (65 to 81) Cognitive impairment: Unclear or Not stated; Assessment by Telephone Inteview For Cogniitive Status. (TICS). Sensory impairment: no details. Medications: Medications at admission- no details for polypharmacy	Matching was carried out on two of the key risk factors (age and cognitive impairment). A matched analysis was carried out with drugs being analysed by a logistic regression method so that the effect of each was obtained independently.	Number key RFs: 2/3 (age, cognitive impairment). Number of pts with delirium at baseline: Not stated; no. pts developing delirium: 91
Agostini 2001; prospective cohort study in 426 patients. Funding: Grant-other. Setting: Hospital; Other ward (unclear/not stated surgery). QUALITY RATING: low	unadjusted RR	2.05 (0.89, 4.74)		Diphenhydramine 114/426 (27%) dose upto 100mg/day. Diphenhydramine given 24h postoperatively	Age: 80 years (73.2 to 86) Cognitive impairment: Cognitive impairment deduced from scores; MMSE at baseline ~23. Sensory impairment: no details. Medications: Antidepressants, antipsychotics, anxiolytic, sedative, and hypnotic drugs. Average number of medications prior to admission about 6.	Age, gender, delirium risk	No.events/no. covariates = 122/4 = 30. Number key RFs: 1/3 (age); patients with profound dementia excluded. Number of pts with delirium at baseline: None with delirium at baseline; 73% intermediate risk of delirum and 28% at high risk; no. pts developing delirium: 9/114

Appendix F: Multivariate risk factors: Pharmacological Risk Factors review

Risk factor: **H2 receptor antagonists**

Outcome measured incidence of delirium

drug: H2-receptor antagonists

Study name	*Outcome*	*Sum stats (95%CI)*	*comments:*	*risk factor details:*	*other details:*	*factors adjusted for in multivariate analysis*	
Pandharipande 2008; prospective cohort study in 100 patients. Funding: Grant-other. Setting: Hospital; ICU ward . QUALITY RATING: low	multivariate adjusted OR	1.71 (0.74, 3.95)		H2 blockers	Age: median 48 y (IQR36 to 60) Cognitive impairment: Unclear or Not stated; . Sensory impairment: visual or hearing impairment not reported. Medications: Sedatives, analgesics, anticholinergics, antipsychotics, general anaesthesia, histamine blockers, antiarrhythmics, NSAIDs, steroids, antidepressants	age, BMI, Charlson comorbidity Index, APACHE II, diagnosis of sepsis, septic shock or ARDS	No.events/no. covariates = 68/7 = 10. Number key RFs: 1/3 (age). Number of pts with delirium at baseline: 68%(positive CAM-ICU during 1st non-comatose eval); no. pts developing delirium: 1st positive CAM-ICUassessment follg a period of normal mental status

Risk factor: **Opioids (continuous variable)**

Outcome measured incidence of delirium

drug: Fentanyl

Study name	*Outcome*	*Sum stats (95%CI)*	*comments:*	*risk factor details:*	*other details:*	*factors adjusted for in multivariate analysis*	
Pandharipande 2006; prospective cohort study in 198 patients. Funding: Grant-other. Setting: Hospital; ICU ward . QUALITY RATING: moderate	multivariate adjusted OR	1.2 (1, 1.5)	The risk in the daily transition to delirium associated with every unit dose of fentanyl(in loge mcg) adminstration in the previous 24h	Fentanyl	Age: 55.5 years (38.5 to 72.5) Cognitive impairment: Cognitive impairment deduced from scores; Blessed Dementia Rating score: 0.2 (SD 0.7); range: 0 to 17. Sensory impairment: 58% visual & 16% hearing impairment. Medications: antipsychotics,anticholinergics, opioids, sedatives	age, gender, visual and hearing deficits, history of dementia, depression, severity of illness [modified APACHE II], sepsis, history of neurologic disease (stroke, epilepsy, other CNS), baseline hematocrit, daily glucose concentration, cognitive status at previous 24 h and medications [lorazepam, midazolam, fentanyl, morphine, propofol]	No.events/no. covariates = 118/17 = 7. Number key RFs: 3/3 (age, sensory impairment, dementia). Number of pts with delirium at baseline: delirium (for those taking antipsychotics)66/75; no. pts developing delirium: during ICU stay: 52/63 those taking anticholinergics; 66/75 those taking antipsychotics

Appendix F: Multivariate risk factors: Pharmacological Risk Factors review

Risk factor: **Opioids (continuous variable)**

Outcome measured incidence of delirium

drug: Morphine

Study name	*Outcome*	*Sum stats (95%CI)*	*comments:*	*risk factor details:*	*other details:*	*factors adjusted for in multivariate analysis*	
Pandharipande 2006; prospective cohort study in 198 patients. Funding: Grant-other. Setting: Hospital; ICU ward . QUALITY RATING: moderate	multivariate adjusted OR	1.1 (0.9, 1.2)	The risk in the daily transition to delirium associated with every unit dose of morphine(in loge mg) adminstration in the previous 24h	Morphine	Age: 55.5 years(38.5 to 72.5) Cognitive impairment: Cognitive impairment deduced from scores; Blessed Dementia Rating score: 0.2 (SD 0.7); range: 0 to 17. Sensory impairment: 58% visual & 16% hearing impairment. Medications: antipsychotics,anticholinergics, opioids, sedatives	age, gender, visual and hearing deficits, history of dementia, depression, severity of illness [modified APACHE II], sepsis, history of neurologic disease (stroke, epilepsy, other CNS), baseline hematocrit, daily glucose concentration, cognitive status at previous 24 h and medications [lorazepam, midazolam, fentanyl, morphine, propofol]	No.events/no. covariates = 118/17 = 7. Number key RFs: 3/3 (age, sensory impairment, dementia). Number of pts with delirium at baseline: delirium (for those taking antipsychotics)66/75; no. pts developing delirium: during ICU stay: 52/63 those taking anticholinergics; 66/75

Risk factor: **Opioids (dichotomous variable)**

Outcome measured incidence of delirium

drug: Meperidine

Study name	*Outcome*	*Sum stats (95%CI)*	*comments:*	*risk factor details:*	*other details:*	*factors adjusted for in multivariate analysis*	
Morrison 2003; prospective cohort study in 541 patients. Funding: Grant-other. Setting: Hospital; Surgical ward . QUALITY RATING: moderate	multivariate adjusted RR	2.4 (1.3, 4.5)		Meperidine	Age: <70: 9%; 70 to 79: 26%; 80+: 65% Cognitive impairment: Some patients with cognitive impairment; 55% [297/541] were cognitively impaired; based on diagnosis or Hx of memory impairment or a dementing illness or made one or more error in 4-item test. Sensory impairment: no details. Medications: benzodiazepines or other sedatives and hypnotics, opioids (including meperidine)	Age, gender (women), residence in nursing home, cognitive impairment, FIM score (2 levels), RAND score (2 levels), Abnormal BP, Abnormal heart rhythm, chest pain, medical complication, morphine (2 levels), meperidine	No.events/no. covariates = 87/16 = 5. Number key RFs: 2/3 (age, cognitive impairment). Number of pts with delirium at baseline: Pts with no delirium at admission enrolled; no. pts developing delirium: 16% [87/541]

Appendix F: Multivariate risk factors: Pharmacological Risk Factors review

Risk factor: **Opioids (dichotomous variable)**

Outcome measured incidence of delirium

drug: Oxycodone

Study name	*Outcome*	*Sum stats (95%CI)*	*comments:*	*risk factor details:*	*other details:*	*factors adjusted for in multivariate analysis*	
Marcantonio 1994; case control study in 245 patients. Funding: Mixed. Setting: Hospital; Surgical ward (likely to be mixed surgery). QUALITY RATING: ----	multivariate adjusted OR	0.7 (0.3, 1.6)	Oxycodone	Oxycodone	Age: 73 years (65 to 81) Cognitive impairment: Unclear or Not stated; Assessment by Telephone Interview for Cognitive Status. (TICS). Sensory impairment: no details. Medications: Medications at admission- no details for polypharmacy	Matching was carried out on two of the key risk factors (age and cognitive impairment). A matched analysis was carried out with drugs being analysed by a logistic regression method so that the effect of each was obtained independently.	Number key RFs: 2/3 (age, cognitive impairment). Number of pts with delirium at baseline: Not stated; no. pts developing delirium: 91

Appendix F: Multivariate risk factors: Pharmacological Risk Factors review

Risk factor: **Opioids**

Outcome measured incidence of delirium

drug: All opioids: Morphine equivalent

Study name	*Outcome*	*Sum stats (95%CI)*	*comments:*	*risk factor details:*	*other details:*	*factors adjusted for in multivariate analysis*	
Morrison 2003; prospective cohort study in 541 patients. Funding: Grant-other. Setting: Hospital; Surgical ward . QUALITY RATING: moderate	multivariate adjusted RR	5.4 (2.4, 12.3)	parenteral morphine suflate equivalents; <10mg/day vs >30 m/day	Parenteral morphine sulfate equivalents: <10mg; 10 to 30 mg; >30mg	Age: <70: 9%; 70 to 79: 26%; 80+: 65% Cognitive impairment: Some patients with cognitive impairment; 55% [297/541] were cognitively impaired; based on diagnosis or Hx of memory impairment or a dementing illness or made one or more error in 4-item test. Sensory impairment: no details. Medications: benzodiazepines or other sedatives and hypnotics, opioids (including meperidine)	Age, gender (women), residence in nursing home, cognitive impairment, FIM score (2 levels), RAND score (2 levels), Abnormal BP, Abnormal heart rhythm, chest pain, medical complication, morphine (2 levels), meperidine	No.events/no. covariates = 87/16 = 5. Number key RFs: 2/3 (age, cognitive impairment). Number of pts with delirium at baseline: Pts with no delirium at admission enrolled; no. pts developing delirium: 16% [87/541]
Morrison 2003; prospective cohort study in 541 patients. Funding: Grant-other. Setting: Hospital; Surgical ward . QUALITY RATING: moderate	multivariate adjusted RR	1.4 (0.6, 3.3)	parenteral morphine suflate equivalents; 10 to 30 mg/day vs >30 m/day	Parenteral morphine sulfate equivalents: <10mg; 10 to 30 mg; >30mg	Age: <70: 9%; 70 to 79: 26%; 80+: 65% Cognitive impairment: Some patients with cognitive impairment; 55% [297/541] were cognitively impaired; based on diagnosis or Hx of memory impairment or a dementing illness or made one or more error in 4-item test. Sensory impairment: no details. Medications: benzodiazepines or other sedatives and hypnotics, opioids (including meperidine)	Age, gender (women), residence in nursing home, cognitive impairment, FIM score (2 levels), RAND score (2 levels), Abnormal BP, Abnormal heart rhythm, chest pain, medical complication, morphine (2 levels), meperidine	No.events/no. covariates = 87/16 = 5. Number key RFs: 2/3 (age, cognitive impairment). Number of pts with delirium at baseline: Pts with no delirium at admission enrolled; no. pts developing delirium: 16% [87/541]

Appendix F: Multivariate risk factors: Pharmacological Risk Factors review

Risk factor: Anaesthesia

Outcome measured incidence of delirium

drug: Anaesthesia

Study name	*Outcome*	*Sum stats (95%CI)*	*comments:*	*risk factor details:*	*other details:*	*factors adjusted for in multivariate analysis*	
Pandharipande 2008; prospective cohort study in 100 patients. Funding: Grant-other. Setting: Hospital; ICU ward . QUALITY RATING: low	multivariate adjusted OR	1.23 (0.37, 4.04)	Odds of transitioning to delirium for patients who received any dose of the given medication in the previous 24h	Anaesthetics	Age: median 48 y (IQR36 to 60) Cognitive impairment: Unclear or Not stated; . Sensory impairment: visual or hearing impairment not reported. Medications: Sedatives, analgesics, anticholinergics, antipsychotics, general anaesthesia, histamine blockers, antiarrhythmics, NSAIDs, steroids, antidepressants	age, BMI, Charlson comorbidity Index, APACHE II, diagnosis of sepsis, septic shock or ARDS	No.events/no. covariates = 68/7 = 10. Number key RFs: 1/3 (age). Number of pts with delirium at baseline: 68%(positive CAM-ICU during 1st non-comatose eval); no. pts developing delirium: 1st positive CAM-ICUassessment follg a period of normal mental status

Risk factor: Benzodiazepines or Opioids

Outcome measured duration of delirium

drug: Benzodiazepines or Opioids

Study name	*Outcome*	*Sum stats (95%CI)*	*comments:*	*risk factor details:*	*other details:*	*factors adjusted for in multivariate analysis*	
Pisani 2009; prospective cohort study in 304 patients. Funding: Grant-other. Setting: Hospital; ICU ward . QUALITY RATING: low	multivariate adjusted RR	1.64 (1.28, 2.11)		continuous: use of benzodiazepines or opiodisduring ICU stay: (77%); 25% had any benzodiazepines or opioids on admission	Age: 75 years (67 to 83) Cognitive impairment: Some patients with cognitive impairment; baseline dementia assessed using IQCODE. Sensory impairment: no details. Medications: benzodiazepine or opiod (81%); medium to high potency ACH (32%), haloperidol (32%), steroid use (52%)	MV: medications (benzodiazepine or opioid use; medium to high potency ACH use; halperidol ause nytime during ICU stay; steroid use anytime during ICU stay), impairment in ADL, depression, dementia, admitting diagnosis of respiratory disease, APACHE II(minus Glasgow Coma Scale), alanine aminotransferase>40 U/l	No.events/no. covariates = 304/10 = 30. Number key RFs: 1/3 (dementia). Number of pts with delirium at baseline: not clear; no. pts developing delirium: 239/304 (79%) developed delirium during ICU stay