

Appendix A.

Protocol Literature Review

| Author             | Study Design                        | Sample size | Patient Pop.   | Outcomes  | Assessment   | Follow-up   | Results   |
|--------------------|-------------------------------------|-------------|--|---|--|---|---|
| Tow et al[1]       | Prospective cohort                  | 142         | Older adults undergoing elective orthopedic surgery  | Incidence and severity of POD   | CAM, Memorial Delirium Assessment Scale, cognitive reserve (literacy and cognitive activities)   | First assessment median 22 hrs postoperatively, second assessment median 32 hrs postoperatively | Greater participation in cognitive activity was associated with lower incidence and severity of delirium  |
| Neufeld et al[2]   | Prospective cohort                  | 91          | Consecutive patients undergoing surgical procedure, ≥ 70 y/o   | Cognitive functioning   | ADLs, IADLs, MMSE, Word Fluency, Digit Span, DSM-IV delirium criteria  | 19 months postoperatively   | No differences in any outcomes between patients with versus without PACU delirium   |
| Sprung et al[3]    | Population based prospective cohort | 1,731       | 70-89 y/o (data abstracted retrospectively for anesthesia exposure from 40 years old until time of evaluation) | Mild cognitive impairment   | 1) impairment in one of the four cognitive domains; 2) cognitive concerns by the subject, informant, examining nurse, or physician; 3) essentially normal functional activities, and; 4) absence of dementia (based on published criteria) | Median 4.8 years  | 31% developed MCI; Cumulative exposure to procedures requiring GA after the age 40 was not associated with the development of incident MCI in cognitively normal elderly participants. Does not exclude possibility that anesthetic exposures occurring later in life may be associated an increase in the rate of incident MCI, especially in patients undergoing vascular surgery |
| Hempenius et al[4] | RCT                                 | 260         | Consecutive patients ≥65 years undergoing surgery for a solid tumor  | mortality, rehospitalization, ADL functioning, return to the independent pre-operative living situation, use of supportive care, cognitive functioning and health related QOL | DOS for delirium, MMSE for cognition   | 3 months  | Geriatric liaison intervention did not improve outcomes. POD was associated with: an increased risk of decline in ADL functioning, an increased use of supportive assistance, and a decreased chance to return to the independent preoperative living situation.  |
| Youngblom et al[5] | Prospective cohort                  | 421         | >65 y/o, noncardiac surgery  | Delirium and POCD   | For delirium: CAM; for POCD: verbal fluency, digit   | 2 days postop   | 80% of patients experienced delirium or POCD on POD1. 48%   |

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|                     |                                    |      |   |   | symbol test, and word list   |  | experienced postoperative delirium on POD1, POD2, or both days. The delirium group had a lower preoperative cognitive status score. incidence of pre-existent dementia was not different between the group that developed delirium and the group that did not. |
| Hussain et al[6]    | Review                             | N/A  | N/A   | Relationship between general anesthesia, major surgery, and dementia, specifically AD | N/A  | N/A  | Future studies need: sufficient sample size, good control group (no anesthesia, no surgery, well-matched otherwise), preop cognitive assessment, maybe use biomarkers for AD.  |
| Abelha et al[7]     | Prospective                        | 562  | SICU patients   | Primary: Mortality<br>Secondary: hospital mortality and "becoming dependent"          | ICDSC for postoperative delirium, SF-36 for health-related QOL   | 6 months   | POD is an independent risk factor for mortality, hospital mortality, and becoming dependent for personal ADLs. Delirium incidence: 16%   |
| Witlox et al[8]     | Prospective cohort nested w/in RCT | 53   | ≥75 years old, hip fracture repair                              | Delirium and postoperative cognitive decline  | Delirium: CAM<br>Cognition: MMSE, the expanded digit span test, and the GDS  | 3 months   | All pts who developed delirium were asked to f/u and an equal number of control pts invited to f/u as well; 5 patients still delirious at 3 months; delirium was associated with impairments in global cognition and episodic memory at follow-up              |
| Radtke et al[9]     | RCT                                | 1155 | ≥60 y/o with at least 60 minute surgery with general anesthesia | Delirium and postoperative cognitive dysfunction                                      | Delirium: DSM IV delirium criteria<br>Cognition: Motor Screening Test, two tests of visual memory and a test of attention, visual verbal learning test and the Stroop Color Word interference test | Assessed for delirium while admitted, f/u at 1 week and 3 months | Delirium incidence was lower in the BIS-monitored group (16.7 vs 21.4%), but POCD was not different in the BIS vs non-BIS group.   |
| Saczynski et al[10] | Prospective cohort                 | 225  | >60 y/o, undergoing CABG or                                     | Delirium and cognition  | Delirium: CAM;<br>Cognition: MMSE  | Delirium assessed starting POD2                                  | Delirium incidence: 43%; Those who developed delirium has a lower  |

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|                      |   |  | valve replacement  |   |  | until pt discharge; Cognitive tests preop and at 1, 6, and 12 months postop | preoperative cognitive score.   |
| Koster et al[11]     | Prospective follow-up study             | 300  | >45 y/o undergoing elective cardiac surgery                        | Delirium, postoperative cognition and functionality, Mortality, readmission | Delirium: DOS scale; Cognition: SF-36, the Cognitive Failure Questionnaire, and a purpose-designed questionnaire       | 6 months  | Delirium incidence: 17%; Delirium was associated w/increased mortality, a higher hospital readmission rate, lower quality of life, cognitive failure, and reduced mobility. |
| Quinlan et al[12]    | Secondary analysis of prospective study | 1218 (948 completed 3 month functional assessment) | Non-cardiac surgery, ≥ 60 y/o                                      | Delirium, cognition, POCD   | MMSE, chart review, ISPOCD neuropsychological tests  | 3 months postoperatively  | After adjustment for age, sex, education, cognition, and surgery duration, delirium remained associated with functional decline   |
| Wallbridge et al[13] | Prospective cohort                      | 89   | Patients undergoing elective abdominal aortic aneurysm surgery y/o | Cognition and function  | Battery of cognitive measures, Portland Adaptability Inventory (PAI) for function                                      | 3 months postoperatively  | Cognitive impairment postoperatively was mild but was associated with number of days delirious and preoperative deficits in verbal memory and psychomotor speed             |
| Jankowski et al[14]  | Prospective cohort                      | 418  | ≥ 65 y/o, undergoing total hip or knee arthroplasty                | Delirium, cognition, function   | CAM, MMSE, neurocognition and functional testing (American National Adult Reading Test, AVLT, COWAT, SCWT, CAGE, IADL) | 3 months postoperatively  | Independent predictors of POD included age, history of psychiatric illness, decreased functional status, and decreased verbal memory  |
| Rudolph et al[15]    | Prospective cohort                      | 190  | ≥ 60 y/o, elective or urgent cardiac surgery                       | Delirium, activities of daily living (function)                             | CAM, IADL  | 1 and 12 months postoperatively   | Delirium associated with functional decline at 1 month and tended toward association at 12 months   |
| Koster et al[16]     | Prospective cohort                      | 112  | Consecutive patients undergoing elective cardiac surgery, ≥ 45 y/o | Delirium, mortality, readmission, cognition, function                       | DSM-IV criteria, study designed questionnaire for cognition  | 1-1.5 years after surgery   | POD associated with increased mortality, readmission, memory and concentration problems, and sleep disturbance  |

|                        |                                       |      |   |   |   |                                     |  |
|------------------------|---------------------------------------|------|---|---|---|-------------------------------------|--|
| Gogol et al[17]        | Review                                | N/A  | N/A   | Cognition, dementia, mortality, functional status                             | N/A   | N/A                                 | Delirium is associated with increased short- and long-term mortality, iatrogenic complications, functional decline, and future development of cognitive impairment or dementia.                            |
| Bickel et al[18]       | Prospective cohort                    | 200  | Consecutive hip surgery patients $\geq 60$ years old                              | Delirium, cognition, mortality, need for long term care                       | MMSE, CAM   | 8 to 38 months postoperatively      | Delirium was a strong independent predictor of cognitive impairment and severe dependency in activities of daily living - more marked long- than for the short-term  |
| Kat et al[19]          | Prospective matched controlled cohort | 112  | Hip surgery patients $\geq 70$ y/o  | Delirium, dementia/mild cognitive impairment (MCI)                            | CAM, MMSE   | 30 months postoperatively           | Delirium associated with increased risk of dementia/MCI, mortality, and institutionalization   |
| Rudolph et al[20]      | Prospective cohort                    | 1218 | Non-cardiac surgery, $\geq 60$ y/o  | Delirium, cognition, POCD   | MMSE, chart review, ISPOCD neuropsychological tests                     | 7 days and 3 months postoperatively | Delirium associated with early but not late POCD   |
| Olofsson et al[21]     | Prospective cohort                    | 61   | Consecutive patients undergoing femoral head fracture operation, $\geq 70$ y/o    | Delirium, LOS, activities of daily living                                     | IADL, Cognition: MMSE, Delirium: OBS, Depression: GDS-15, PGCMS, S-COVS | 4 months postoperatively            | Delirium incidence: 68%. Delirium was associated with more dementia and depression before their fractures, longer LOS after surgery, and more dependence before surgery, on discharge, and at 4 month f/u. |
| Rothenhauser et al[22] | Prospective cohort                    | 30   | Patients undergoing cardiac surgery with CPB                                      | Cognition, depression, posttraumatic stress symptoms, health status, delirium | Syndrom Kurztest, SF-36, Delirium Rating Scale (DRS)                    | 1 year postoperatively              | Lower cognition associated with lower HRQOL  |
| Duppils et al[23]      | Prospective cohort                    | 115  | $\geq 65$ y/o, prior participation in observational hip fracture - delirium study | Delirium, cognition, quality of life  | DMS-IV criteria for delirium, MMSE, SF-36                               | 6 months postoperatively            | Delirium associated w/ greater cognitive deterioration in hospital, lower health-related quality of life at follow up  |
| Edelstein et al[24]    | Prospective cohort                    | 921  | $\geq 65$ y/o, operatively treated hip fracture                                   | Postoperative complication rates, in-hospital                                 |   | 1 year follow up                    | POD incidence: 5.1%. Patients w/ POD had longer LOS, higher 1 year mortality, less likely to   |

|                     |                      |     |   |   |  |                                |   |
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|                     |                      |     |   | mortality, hospital LOS, hospital discharge status, 1-year mortality rate, place of residence, recovery of ambulatory ability, and activities of daily living |  |                                | recover level of ambulation, more likely to show a decline independence. No difference in postoperative complications, in-hospital mortality, discharge residence, and recovery of instrumental activities of daily living at 1 year. |
| Adunsky et al[25]   | Retrospective cohort | 281 | Elderly hip fracture patients   | Cognition, delirium, function   | MMSE, CAM, functional independence measure (FIM)                 | 1 week postop and at discharge | Delirium patients tend to be more disabled and more cognitively impaired  |
| Lundstrom et al[26] | Prospective cohort   | 78  | ≥ 65 y/o, non-demented, femoral neck fracture                                 | Dementia and mortality  | Organic Brain Syndrome (OBS) scale and MMSE                      | 5 year follow up               | Increased dementia and mortality in patients with POD vs. not   |
| Edlund et al[27]    | Prospective cohort   | 54  | Consecutive patients admitted for femoral neck fractures, age range 40-98 y/o | Postoperative delirium incidence  | OBS  | 6 months follow up             | POD incidence: 27.8%. Dementia & increased surgery wait time = greater POD incidence; delirium = worse outcomes after surgery   |
| Goldstein et al[28] | Prospective cohort   | 362 | General surgical, orthopedic, non-surgical, ≥ 55 y/o                          | Postoperative decline   | Psychosocial questionnaire, tests of cognition, affect, function | 10 months postoperatively      | No significant contribution to changes from baseline  |

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