März 2017/ib

# Forschungsprojekte nationaler Tragweite
## Vorlage für das Einreichen eines Projekts

# Ausschreibung Nr. 8

**Die Beschreibung des Projekts darf nicht länger als 5 Seiten sein**

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| **Titel des Projekts** | Detection and prevention of delirium triggered by adverse drug events | | **Datum** **28.4.2017** |
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| **Identifiziertes Problem und Bedeutung des Problems in der Schweiz** | Medication therapy can lead to unintended iatrogenic consequences [1,2], also known as adverse drug events (ADEs), accounting for one-third (10% to 40%) of all hospital care-related adverse events [3-7]. According to the literature, between 0.2% and 65% of hospitalized patients experience at least one ADE during their stay [2,3,7-13]. Apart from increasing patient morbidity and mortality, ADEs are known to increase the length of stay, risk for readmission as well as costs [2,4,9,14,15,18-20]. Approximately, 20-50% of all ADEs are deemed preventable (pADEs) [3,9,21]. pADEs are more frequently serious and associated with increased length of stay and costs than non-preventable ADEs [2,4,9,10,20].<br>In older institutionalized patients, neuropsychiatric events (e.g. sedation, confusion, hallucinations, delirium) comprise the most common type of pADEs [22]. | | |

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| | Delirium is an acute and fluctuating state of confusion and disorientation, characterized by changes in attention, cognition, consciousness, and perception, and is often associated with changes in sleep patterns. It occurs in 0.4% to 2% of the general population [23,24], and the prevalence increases with age to 14% of persons 85 years old or older [23]. Delirium is particularly prevalent among hospitalized elderly persons, occurring in 20%–60% and contributing to $6.9 billion (2004 U.S. dollars) in Medicare hospital costs annually [25]. Up to 80% of critically ill patients experience delirium [26]. It significantly increases the risk for medical complications, institutionalization, functional decline, and dementia [27,28]. Delirium is also linked to longer ICU stay, longer hospital stay, and higher mortality [26,29].<br>Many factors have been associated with increased risk of delirium, including age, cognitive impairment, comorbidity, depression, smoking, alcohol, visual and hearing impairment, ASA-score, biochemical abnormalities, operative strategies, blood loss and drugs [30]. In the context of ADEs, delirium has been shown to be one of the most preventable conditions in elderly hospitalized patients. Studies indicate that at least 30%–40% of cases of patients with delirium may be preventable [24].<br>Han et al. showed that anticholinergic medication is associated with a subsequent increase in delirium symptom severity in elderly medical inpatients with diagnosed delirium [31]. Elevated anticholinergic activity has also been positively correlated with delirium symptom severity, indicating a dose-response relationship [32].<br>In our own study, we observed that intensive care patients with delirium had a higher anticholinergic drug burden than those without delirium ($p < 0.01$) [33]. This drug-drug interaction (DDI) was often not noted by interaction check systems (e.g. mediQ, Pharmavista). Drug-induced delirium may therefore remain unrecognized.<br>For the treatment of delirium, neuroleptics such as haloperidol or quetiapine are often used. Their use is off label and comprises a lot of risks, especially arrhythmia and extrapyramidal symptoms [34,35]. They have also been associated with an increased risk of sudden death and stroke [35]. There are several new studies with melatonin to prevent and treat delirium, however with contradictory effects [36].<br>Detection and prevention of drug induced delirium will therefore improve patient outcome, reduce health care use and costs and avoid unnecessary and potentially harmful pharmacological treatment. |
| Literatur<br><br>Analyse von Literaturdaten | Many interventions have been conducted to improve the quality and safety of prescribing [4,37-40]. The most recent and significant ones include the provision of evidence-based prevention tools (e.g. specific guidelines [41], lists of potentially inappropriate medication criteria [42-44), pharmacist-based interventions (e.g. patient counselling, medication reconciliation, clinical pharmacist rounding) [45,46], team-based interventions (e.g. multidisciplinary geriatric teams [38]), and information and communication technologies such as clinical decision support (CDS) tools within computer provider order entry (CPOE) systems [47]. Combined and interdisciplinary interventions often yielded the best effects [48].<br>According to a Cochrane review, there is only limited evidence that would support successful interventions to prevent delirium in older people [49]. A large randomized controlled trial in U.S. long term care institutions assessed the effect of a computerized system to identify drugs which may contribute to delirium risk and trigger a pharmacist-led medication review [49]. They reported a large reduction in delirium incidence but no significant effect on hospital admissions, mortality or fall risks. Another study, testing multi-factorial interventions, which did not target only drug use, had positive effects [50]. Extrapolation of these results to Swiss systems and hospitals may be difficult.<br>In a potentially under-powered study by Khan et al., a clinical decision support system did not reduce the incidence of delirium in cognitively impaired older adults transferred to an intensive care unit [51].<br>To our knowledge, no study trying to reduce drug induced delirium has been performed in Switzerland. |
| **Zielsetzungen des Projekts**<br><br>**Hypothese**<br>**Begründung**<br>**Erwartete Ergebnisse**<br>**Auswirkung für die Praxis** | 1. To detect drug induced delirium and identify risk factors in different population groups<br>2. To prevent drug induced delirium by automatically calculating anticholinergic burden of drug therapy, displaying alerts in CPOE and automatically directing daily lists of orders with candidate medications to experts for review |

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| **Beschreibung der Methode**<br>**Protokoll, Methode, Analyse der Ergebnisse, Statistik** | 1. Based on a literature search, an anticholinergic score is attributed to each drug. A chart review is performed on wards of internal medicine (especially on the geriatric ward), surgery, and the intensive care unit (ICU). On the ICU, the nursing personal systematically and routinely screens all patients two times a day for delirium using the ICDSC-scale (Intensive Care Delirium Screening Checklist). On the other wards, the DOS (delirium observation scale) is integrated in the electronic patient record. These data are easily available. The total anticholinergic score of each patient's therapy is calculated and matched with the occurrence of delirium. Risk factors like drug-drug interactions, renal failure, surgery, and age are collected from the patient records. The anticholinergic score of patients with and without delirium is compared by using unpaired t-test or Mann-Whitney-U-test. Risk factors are assessed by univariable and multivariable cox proportional hazards regression analysis.<br><br>2. An algorithm using the anticholinergic score and other risk factors will be developed and tested on a database used for a project of the Swiss National Foundation (see below and http://www.nfp74.ch/en/projects/all-projects). The algorithm is then implemented in the hospital's CPOE (KISIM). It includes automatic mailing lists to experts (e.g. clinical pharmacists, delirium expert group) for review and patient-specific advice. The impact of the implemented tool is tested either by comparison with phase 1 or - if feasible - by a randomized controlled trial. For comparison of the two groups, either contingency tables and Fisher's exact test (for nominal data) or Mann-Whitney-U-Tests (for continuous data) will be used.<br><br>Statistical significance is calculated with 1-β=0.8 and α=0.05 and a two-sided hypothesis. "SPSS" and "*R*" are used for statistical analysis.<br>The project will be submitted to the ethical committee for approval (EKNZ). |
| **Ort (e) der Studie**<br>**Institute, die am Forschungsprojekt teilnehmen** | Kantonsspital Baden<br>• Spitalapotheke, Dr. P. Wiedemeier<br>• Chirurgie, Prof. A. Nocito<br>• Intensivmedizin, Prof. M. Heesen<br>• Innere Medizin, Prof. J. Beer<br>Universitätsspital Zürich<br>• Klinische Pharmakologie, Dr. P. Beeler |
| **Outcomes**<br>**Erwartete Hauptergebnisse** | **Ad 1:**<br>• Anticholinergic burden of drug therapy<br>• Delirium incidence<br>• Association of anticholinergic drug burden and incidence of delirium<br>• Other risk factors associated with delirium<br>**Ad 2: in intervention group vs. control group:**<br>• Delirium incidence<br>• Severity and duration of delirium<br>• Use of medication for delirium (e.g. neuroleptics, sedativa and melatonin)<br>• Length of stay<br>• Rehospitalisation rate |
| **Nationale Tragweite**<br>**Aspekte hervorheben, die einen nationalen Impact rechtfertigen (z.B. Bedeutung der Ergebnisse, multizentrisch, interdisziplinär)** | Delirium is a frequent and serious ADE in hospitals. Its prevention may reduce length of hospital stay, mortality and costs, and avoid unnecessary and potentially harmful pharmacological treatment.<br>The manual algorithm (checklist) and automated algorithm (source code) can be implemented in other hospitals, and be used by clinical pharmacists.<br>The project is associated with a large interdisciplinary, multicentric research project financed by the Swiss National Foundation (NRP 74, "Automatic detection of adverse drug events in the geriatric care", http://www.nfp74.ch/en/projects/all-projects) where pharmacists, clinical pharmacologists, geriatricians, epidemiologists, specialists in medical informatics, structured data mining and natural language processing closely work together. The experience gained with this project will facilitate the development of other algorithms to prevent ADEs. |

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| **Planung**<br>**Vorgesehener Zeitplan**<br>**Etappen (milestones)** | Duration: 3 years (2018-2020)<br>2018: Project submission to the ethical committee<br>Literature search<br>Chart review<br>2019: Development and implementation of the algorithm<br>Preparation intervention study<br>Publication results chart review<br>2020: Comparison of delirium incidence in intervention group vs. control group<br>Publication intervention study |
| **Finanzierung**<br>**Notwendiger Betrag**<br>**Verwendung**<br>**Andere Finanzierungsquellen** | The grant is aimed to pay a PhD student over at least 3 years.<br>One part is covered by a 20% pharmacist position at Kantonsspital Baden (3 years = ca. 64'000 including social costs). 49'290 CHF are paid by the SNF project "Automatic detection of adverse drug events in the geriatric care" (http://www.nfp74.ch/en/projects/all-projects).<br>To achieve a total salary of 170'000 CHF (according to SNF including social costs) we still need about 58'000 CHF. |

**References:**


1. Nebeker JR, Barach P, Samore MH. Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. Ann Intern Med 2004; 140(10):795-801
2. Krahenbuhl-Melcher A, Schlienger R, Lampert M, Haschke M, Drewe J, Krahenbuhl S. Drug-related problems in hospitals: a review of the recent literature. Drug safety 2007; 30(5):379-407
3. de Vries EN, Ramrattan MA, Smorenburg SM, et al. The incidence and nature of in-hospital adverse events: a systematic review. Qual Saf Health Care 2008; 17(3):216-23
4. US Department of Health Human Services. National action plan for adverse drug event prevention. Washington, DC 2014
5. Jha AK, Larizgoitia I, Audera-Lopez C, Prasopa-Plaizier N, Waters H, Bates DW. The global burden of unsafe medical care: analytic modelling of observational studies. BMJ quality & safety 2013; 22(10):809-15
6. Leape LL, Brennan TA, Laird N, Lawthers AG, Localio AR, Barnes BA, et al. The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. N Engl J Med 1991; 324(6):377-84
7. Bouvy JC, De Bruin ML, Koopmanschap MA. Epidemiology of adverse drug reactions in Europe: a review of recent observational studies. Drug safety 2015; 38(5):437-53
8. Klopotowska JE, Wierenga PC, Smorenburg SM, Stuijt CC, Arisz L, Kuks PF, et al. Recognition of adverse drug events in older hospitalized medical patients. European journal of clinical pharmacology 2013; 69(1):75-85
9. Levinson DR, General I. Adverse events in hospitals: national incidence among Medicare beneficiaries. Department of Health and Human Services Office of the Inspector General, 2010
10. Boeker EB, Ram K, Klopotowska JE, et al. An individual patient data meta-analysis on factors associated with adverse drug events in surgical and non-surgical inpatients. British journal of clinical pharmacology 2015; 79(4):548-57
11. Classen DC, Resar R, Griffin F, Federico F, Frankel T, Kimmel N, et al. 'Global trigger tool' shows that adverse events in hospitals may be ten times greater than previously measured. Health Aff (Millwood) 2011; 30(4):581-9
12. Davies EC, Green CF, Taylor S, et al. Adverse drug reactions in hospital in-patients: a prospective analysis of 3695 patient-episodes. PloS one 2009; 4(2):e4439
13. Martins AC, Giordani F, Rozenfeld S. Adverse drug events among adult inpatients: a meta-analysis of observational studies. J Clin Pharm Ther 2014; 39(6):609-20
14. Alhawassi TM, Krass I, Bajorek BV, Pont LG. A systematic review of the prevalence and risk factors for adverse drug reactions in the elderly in the acute care setting. Clin Interv Aging 2014; 9:2079-86
15. Classen DC, Pestotnik SL, Evans RS, Lloyd JF, Burke JP. Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality. JAMA 1997; 277(4):301-6
16. Klopotowska JE, Wierenga PC, Stuijt CC, et al. Adverse drug events in older hospitalized patients: results and reliability of a comprehensive and structured identification strategy. PloS one. 2013; 8(8):e71045
17. Kaufmann CP, Stämpfli D, Hersberger KE, Lampert ML. Determination of risk factors for drug-related problems: a multidisciplinary triangulation process. BMJ Open 2015 ;5(3):e006376
18. Christensen M, Lundh A. Medication review in hospitalised patients to reduce morbidity and mortality. The Cochrane database of systematic reviews 2013; 2:Cd008986
19. Classen DC, Pestotnik SL, Evans RS, Burke JP. Computerized surveillance of adverse drug events in hospital patients. JAMA 1991; 266(20):2847-51
20. Hug BL, Keohane C, Seger DL, Yoon C, Bates DW. The costs of adverse drug events in community hospitals. Jt Comm J Qual Patient Saf 2012; 38(3):120-6
21. Bates DW, Cullen DJ, Laird N, et al. Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group. JAMA 1995; 274(1):29

22. Gurwitz JH, Filed TS, Judge J, et al. The incidence of adverse durg events in two large academic longterm care facilities. Am J Med 2005; 118(3):251
23. Inouye SK. Delirium in older persons. N Engl J Med 2006; 354:1157–1165
24. Folstein M, Bassett S, Romanoski A, Nestadt G. The Epidemiology of Delirium in the Community: The Eastern Baltimore Mental Health Survey. International Psychogeriatrics 1991; 3(2):169-176
25. Inouye SK, Bogardus ST, Jr, Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med 1999; 340:669–676
26. Ely EW, Gautam S, Margolin R, et al. The impact of delirium in the intensive care unit on hospital length of stay. Intensive Care Med 2001; 27:1892–1900
27. Pitkala KH, Laurila JV, Strandberg TE, Tilvis RS. Multicomponent geriatric intervention for elderly inpatients with delirium: a randomized, controlled trial. J Gerontol A Biol Sci Med Sci 2006; 61:176–181
28. Bellelli G, Speciale S, Barisione E, Trabucchi M. Delirium subtypes and 1-year mortality among elderly patients discharged from a post-acute rehabilitation facility. J Gerontol A Biol Sci Med Sci 2007; 62:1182–1183
29. Ouimet S, Kavanagh BP, Gottfried SB, et al. Incidence, risk factors and consequences of ICU delirium. Intensive Care Med 2007; 33:66
30. Jackson TA, Wilson D, Richardson S, Lord JM. Predicting outcome in older hospital patients with delirium: a systematic literature review. Int J Geriatr Psychiatry 2016; 31(4):392-9
31. Han L, McCusker J, Cole M, Abrahamowicz M, et al. Use of medications with anticholinergic effect predicts clinical severity of delirium symptoms in older medical inpatients. Arch Intern Med 2001; 161:1099–1105
32. Flacker JM, Cummings V, Mach JR, Jr, et al. The association of serum anticholinergic activity with delirium in elderly medical patients. Am J Geriatr Psychiatry 1998 ; 6:31–41
33. Endres K, Siegemund M, Wiedemeier P, Lutters M. Polypharmazie als Risiko für Delir und QT-Zeitverlängerung auf der Intensivstation, presented at the GSASA-Kongress 2014 in Interlaken
34. https://compendium.ch
35. Maust DT, Kim HM, Seyfried LS, et al. Antipsychotics, Other Psychotropics, and the Risk of Death in Patients With Dementia. Number Needed to Harm. JAMA Psychiatry 2015; 72(5):438-445
36. Walker CK, Gales MA. Melatonin Receptor Agonists for Delirium Prevention. Ann Pharmacother 2016; pii: 1060028016665863. [Epub ahead of print]
37. Spinewine A, Schmader KE, Barber N, et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? Lancet 2007; 370(9582):173-84
38. Topinkova E, Baeyens JP, Michel JP, Lang PO. Evidence-based strategies for the optimization of pharmacotherapy in older people. Drugs & Aging 2012; 29(6):477-94
39. Medicine Io. Preventing Medication Errors: Quality Chasm Series. Aspden P, Wolcott J, Bootman JL, Cronenwett LR, editors. Washington, DC: The National Academies Press; 2007, p. 480
40. Cooper JA, Cadogan CA, Patterson SM, Kerse N, Bradley MC, Ryan C, et al. Interventions to improve the appropriate use of polypharmacy in older people: a Cochrane systematic review. BMJ Open 2015; 5(12):e009235
41. Onder G, Landi F, Fusco D, Corsonello A, Tosato M, Battaglia M, et al. Recommendations to prescribe in complex older adults: results of the CRIteria to assess appropriate Medication use among Elderly complex patients (CRIME) project. Drugs & Aging 2014; 31(1):33-45
42. Renom-Guiteras A, Meyer G, Thurmann PA. The EU(7)-PIM list: a list of potentially inappropriate medications for older people consented by experts from seven European countries. European journal of clinical pharmacology 2015; 71(7):861-75
43. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. Journal of the American Geriatrics Society 2015; 63(11): 2227-46
44. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing 2015; 44(2):213-8
45. Schnipper JL, Kirwin JL, Cotugno MC, et al. Role of Pharmacist Counseling in Preventing Adverse Drug Events After Hospitalization. Arch Intern Med 2006; 166(5):565-571
46. Glassman P. Clinical Pharmacist's Role in Preventing Adverse Drug Events: Brief Update Review. Making Health Care Safer II: An Updated Critical Analysis of the Evidence for Patient Safety Practices. Evid Rep Technol Assess No. 211 (Full Rep). Rockville (MD): Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services; 2013, p. 518
47. Yourman L, Concato J, Agostini JV. Use of computer decision support interventions to improve medication prescribing in older adults: a systematic review. Am J Geriatr Pharmacother 2008; 6(2):119-29
48. Lutters M, Harbarth S, Janssens JP, Freudiger H, Herrmann F, Michel JP, Vogt N. Effect of a Comprehensive, Multidisciplinary, Educational Program on the Use of Antibiotics in a Geriatric University Hospital. Journal of the American Geriatrics Society 2004; 52(1):112-6
49. Clegg A, Siddiqi N, Heaven A, Young J, Holt R. Interventions for preventing delirium in older people in institutional long-term care. Cochrane Database Syst Rev. 2014; 1:CD009537
50. Börkelund KB, Hommel A, Thorngren KG et al. Reducing delirium in elderly patients with hip fracture: a multi-factorial intervention study. Acta Anaesthesiol Scand 2010; 54(6):678-88

51. Khan BA, Calvo-Ayala E, Campbell N, et al. Clinical Decision Support System and Incidence of Delirium in Cognitively Impaired Older Adults Transferred to Intensive Care. American journal of critical care 2013; 22(3):257-262