Appendix to the AID-ICU cohort study protocol

Statistical Analysis Plan dated 17/03 2017

Data presentation: Numeric data will be shown as medians with inter-quartile ranges (IQR) or ranges where relevant. Frequencies will be shown as numbers with percentages and 95% confidence intervals (CI) where relevant.

We will present the number of patients receiving haloperidol at any time during ICU stay (overall, those receiving regular doses only, those receiving as needed doses (PRN), and both dosing methods as frequencies (% with 95% CI). We will present the overall cumulative dose given in ICU, those receiving regular doses only, those receiving as needed doses (PRN), and both dosing method. We will report ICU length of stay before first dose of haloperidol and the number of days haloperidol was administrated. The number of patients receiving haloperidol, and additional delirium treatment agents, anti-psychotics, benzodiazepines and rivastigmine are recorded.

We will compare differences in baseline characteristics between patients receiving and not receiving haloperidol using Wilcoxon's or Chi-square test.

We will present the number of patients receiving the other anti-psychotics, benzodiazepines, opioids, sedatives and sleeping pills as frequencies (% with 95% CI).

We will present the number of patients with active, hypoactive and mixed type of delirium, and use of physical restraints as frequencies (% with 95% CI). We will report the numbers of days with delirium and use of restraints (medians (IQR)) and present use of interventions per subtype of delirium.

We will present the number of patients who received continuous infusion of sedatives, opioids and life support including the median (IQR) number of days.

Outcomes:
Primary outcome: Number of patients with any form of delirium treated with haloperidol will be presented as a frequency (%) with 95% CI.

Secondary outcomes:
- Number of ICU patients with delirium intervened with other antipsychotics than haloperidol
- Number of patients with delirium
- Mortality at 90 days
- Days alive without mechanical ventilation and days alive out of hospital (ICU) in a 90-day period

These will be presented for all patients and those not receiving haloperidol, those receiving haloperidol and those with delirium receiving haloperidol.
-To assess risk factors for the use of haloperidol in ICU, we will do a multiple logistic regression analysis including patient baseline (1st day in ICU) characteristics (age (in quartiles), presence of delirium as no, hyper, hypo or mixed, use of dialysis (y/n), shock (y/n), use of mechanical ventilation (y/n)), use of sedation (y/n) and ICU characteristic (university hospital, guidelines for identifying and/or treating delirium and average staff-patient ratio as 1:1, 1:2, 1:3 or 1:3+).

-To assess if haloperidol is associated predictor of 90-day mortality, we will do multivariate analysis including patient baseline (1st day in ICU) characteristics (age, use of haloperidol, use of dialysis, use of vasopressor/inotrope, use of mechanical ventilation and the present of delirium as no, hyper, hypo or mixed).

For both these adjusted analyses, we will use the 24-h baseline covariates in the primary analyses and do supplementary analyses employing 'new baselines' using the occurrence of the covariates from 0 to 72-hours and from 0-hour to 1-week. In these analyses we will only analyse patients who were still in the ICU at 72 hours and 1-week, respectively.

-Based on the 90-day follow-up period, we will do exploratory analyses on the interaction between delirium (subtype) and use of haloperidol according to patient-relevant outcomes measure such as 1) days alive without mechanical ventilation, 2) days alive out for hospital, 3) days without coma or delirium. These will be reported as rates: (days on ventilation/ days alive in the 90-day observation period), (days out of hospital/days alive in the 90-day observation period), (days without coma or delirium/days alive in the 90-day observation period) and the primary analyses will be simple comparisons between groups. When concluding on the rates, we will take any difference in underlying mortality into account.

All statistical tests will be 2-tailed and $p<.05$ considered statistically significant.

Missing data will be presented in the appendix of the main manuscript. We expect only few individuals with missing data therefore we will employ complete case analyses after logical imputations. All details will be presented in a supplement to the primary publication. For missing 90-day mortality data, we will assume that patients were alive if they were discharged from ICU or hospital alive. We will do supplement analyses assuming that these patients had died.