Supplementary File 1

Detailed explanation of sample size calculations

The following parameters were considered in the samples size calculation strategy and confirmations:

Parameter		Explanation / justification
Proportions	**% delirium within 7 days**	
Placebo	30 %	Proportion of patients experiencing postoperative delirium after open heart surgery for all ages has been reported to be 24%,[1] and higher in the elderly.[2] With participants over 70 years in this trial, we expect the proportion to be at least 30%.
Dexmedetomidine (DEX)	15 %	Recent meta-analysis indicated dexmedetomidine approximately halves the risk of delirium[3]
Clonidine	20 %	Clonidine is anticipated to have similar effect to DEX, however 10 percentage point reduction would also be clinically significant
Power	80 %	
Significance level	5 %	
Duration of follow-up	7-days	
Accrual period	0-days*	

*Observation period starts with operation for all participants

Conservative sample size: As described the initial, conservative samples size calculation based on comparison of two proportions indicated that a sample size of 290 in each group (870 altogether) will give a power of 80% with a significance level of 5% to detect such a difference between of 20 % delirium in the clonidine and 30 % in the placebo group in the proportion developing delirium within 7 days postoperatively. To account for dropouts, we aim at including 900 patients.

This sample size calculation approach was conservative considering the use of time-to-delirium analysis strategy, accommodating for a higher drop-out rate. Furthermore, the study will be more than adequately powered to find the greater expected reduction in delirium in the dexmedetomidine group.

Since we intend to use the logrank test to account for difference in the observation period, we confirmed that the calculated sample size was adequate using the more flexible calculation options in PASS Sample size software (version 20, NCSS, Kaysville, Utah, USA).

Logrank test: A two-sided logrank test with an overall sample size of 498 subjects (249 in the control group and 249 in the treatment group) achieves 80 % power at a 5 % significance level to a reduction in the proportion with delirium from 30 % in the control arm to 20 % in the clonidine arm (equivalent to a hazard ratio of 1.34). By including 300 participants in each group, we will still achieve 80 % power with up to 7 % drop-out rate over the first seven postoperative days. Drop out rates lower than 7 % will result in a higher power. Even with 10 % drop out rate, we will still achieve 80 % to detect a slightly larger difference between the groups (10.4 percentage point reduction, rather than 10 percentage points) (Figure S1).

Multiplicity: The planned comparisons for this trial are between dexmedetomidine versus placebo and clonidine versus placebo. Any comparison between dexmedetomidine and clonidine groups will be explorative and clearly stated as such. The extension of the CONSORT 2010 Statement for multi-arm parallel-group randomised trials recommend that adjustments for multiple comparisons are generally not necessary in trials comparing two or more independent treatments to placebo as we are here.[4] This has therefore not been factored into the sample size calculation. However, even with the very conservative Bonferroni adjustment for two comparisons a sample size of 300 participants per arm will be sufficient if there were no drop-outs and only minimally affect the difference in proportions which we can hope to identify with 80 % power if there is up to 10 % drop-out (Figure S1). For example, with 5 % dropout we can detect a 10.6 percentage point reduction in delirium cumulative incidence with 80 % and 2.5 % significance level (to account for multiplicity), or 11.3 percentage points if there was 10 % dropout (Figure S1).

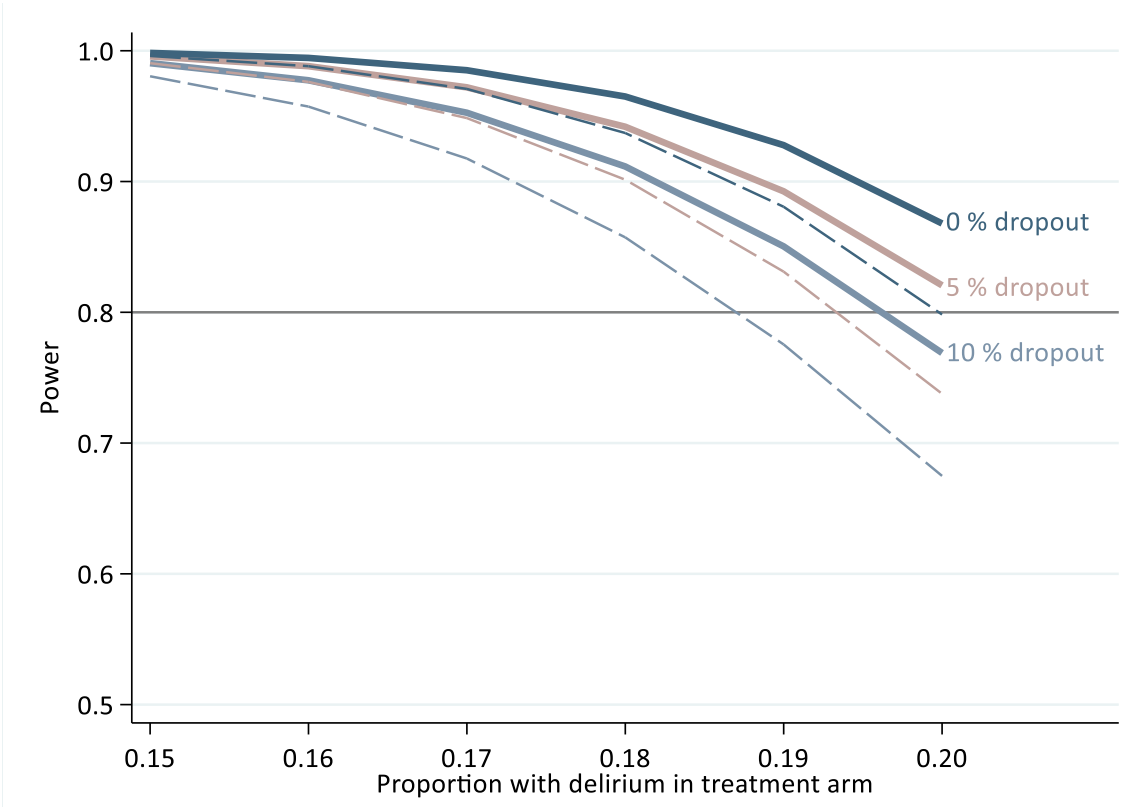

Figure S1: Power depending differing drop-out rates over the proportion with delirium in the treatment arm and where the proportion in the control arm is 30 %. The solid lines indicate the power with 5 % significance level for studies with no dropout (dark blue), 5 % dropout (pink) or 10 % dropout (medium blue). The corresponding broken lines indicate the power with 2.5 % significance level, a Bonferroni adjustment for the two planned comparisons.

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2. Eide LS, Ranhoff AH, Fridlund B, et al. Comparison of frequency, risk factors, and time course of postoperative delirium in octogenarians after transcatheter aortic valve implantation versus surgical aortic valve replacement. *The American journal of cardiology* 2015;115(6):802-9. doi: 10.1016/j.amjcard.2014.12.043 [published Online First: 2015/02/04]
3. Flukiger J, Hollinger A, Speich B, et al. Dexmedetomidine in prevention and treatment of postoperative and intensive care unit delirium: a systematic review and meta-analysis. *Annals of intensive care* 2018;8(1):92. doi: 10.1186/s13613-018-0437-z [published Online First: 2018/09/22]
4. Juszczak E, Altman DG, Hopewell S, et al. Reporting of Multi-Arm Parallel-Group Randomized Trials: Extension of the CONSORT 2010 Statement. *JAMA* 2019;321(16):1610-20. doi: 10.1001/jama.2019.3087