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Efficacy of halopeRIdol to decrease the burden of Delirium In adult Critically ill patiEnts (EuRIDICE): study protocol for a prospective randomised multi-center double-blind placebo-controlled clinical trial

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1	Efficacy of halopekidol to decrease the burden of Delirium in adult
2	Critically ill patiEnts (EuRIDICE): study protocol for a prospective
3	randomised multi-center double-blind placebo-controlled clinical
4	trial
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13 14	34	Protocol version: N
15 16	35	
17 18	36	Word count: 4326 v
19 20	37	
21 22 23	38	ABSTRACT
23 24 25	39	Introduction: Deliriu
26 27	40	increased mortality a
28 29	41	recommendations ad
30 31	42	routine use of sched
32 33	43	evidence regarding i
34 35	44	outcomes. This stud
36 37	45	of delirium in adult c
38 39	46	Methods and analy
40 41 42	47	placebo-controlled, t
42 43	48	neurologic injury whe
44 45 46	49	Checklist (ICDSC) o
40 47 48	50	Intervention is intrav
49 50	51	daily based on ICDS
51 52	52	delirium resolution o
53 54	53	coma (DCFD) up to
55 56	54	1-year mortality; 2) c
57 58	55	family delirium and l
59 60	56	safety concerns asso

E-mail: m.vanderjagt@erasmusmc.nl Telephone number: +31107040704 Protocol version: November 16th 2017, Version 2 Word count: 4326 words ABSTRACT Introduction: Delirium in critically ill adults is associated with prolonged hospital stay, increased mortality and greater cognitive and functional decline. Current practice guideline recommendations advocate the use of non-pharmacologic strategies to reduce delirium. The routine use of scheduled haloperidol to treat delirium is not recommended given a lack of evidence regarding its ability to resolve delirium nor improve relevant short and longer-term outcomes. This study aims to evaluate the efficacy and safety of haloperidol for the treatment of delirium in adult critically ill patients to reduce days spent with coma or delirium. Methods and analysis: EuRIDICE is a prospective, multicentre, randomized, double-blind, placebo-controlled, trial. Study population consists of adult ICU patients without acute neurologic injury who have delirium based on a positive Intensive Care Delirium Screening Checklist (ICDSC) or Confusion Assessment Method for the ICU (CAM-ICU) assessment. Intervention is intravenous haloperidol 2.5 mg (or matching placebo) every 8 hours, titrated daily based on ICDSC or CAM-ICU positivity to a maximum of 5 mg every 8 hours, until delirium resolution or ICU discharge. Main study endpoint is ICU days free of delirium and coma (DCFD) up to 14 days after randomisation. Secondary endpoints include 1) 28-day and 1-year mortality; 2) cognitive and functional performance at 3 and 12 months; 3) patient- and family delirium and ICU experience; 4) psychological sequelae during and after ICU stay; 4) safety concerns associated with haloperidol use; and 5) cost-effectiveness. Differences in

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2 3	57	DCEDs between belongridel and placebo group will be applyined using Deisson regression
4 5	57	berbs between halopendol and placebo group will be analysed dsing Poisson regression
6	58	analysis. Study recruitment started in February 2018 and continues.
/ 8	59	Ethics and dissemination: The study has been approved by the Medical Ethics Committee
9 10	60	of the Erasmus University Medical Centre Rotterdam (MEC2017-511). Its results will be
11 12	61	disseminated via peer-reviewed publication and conference presentations.
13 14	62	Trial registration: ClinicalTrials, NCT03628391. Registered 14 August 2018 -
15 16 17	63	https://clinicaltrials.gov/ct2/show/NCT03628391.
17 18 10	64	
20 21	65	Strengths and limitations of this study
22 23	66	- This study is the first European sufficiently powered randomised multi-center
24 25	67	double-blind placebo-controlled clinical trial;
26 27	68	- Extensive neurocognitive testing will be conducted with a valid test battery in
28 29	69	order to assess cognitive impairment at 3 and 12 months after ICU admission;
30 31	70	- We will assess patient- and family experiences associated with delirium as a
32 33	71	novel outcome;
34 35	72	
36 37	73	INTRODUCTION
38 39 40	74	Delirium occurs in up to 80% of patients admitted to the Intensive Care Unit (ICU) (1, 2) and
40 41 42	75	is associated with greater ICU and post-ICU mortality (2). Cognitive dysfunction and
43 44	76	functional decline after critical illness is common, frequently persists for months after ICU
45 46	77	discharge, and is worse among patients who experience delirium (2, 3). The symptoms and
47 48	78	sequelae of delirium, including fear, anxiety, disrupted sleep, and post-traumatic stress
49 50	79	disorder, may persist for months after ICU discharge. The health and societal costs of
51 52	80	delirium are estimated to exceed \$10 billion per year in the USA alone (4).
53 54	81	Given the burden and costs of delirium in critically ill adults, substantial research
55 56	82	efforts have been devoted to identify safe and effective strategies to treat it. Current evidence
57 58	83	and practice guideline recommendations advocate the use of non-pharmacologic strategies
60 60	84	to reduce delirium, including avoidance of benzodiazepine sedation, early mobilization and

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the use of sleep improvement protocols. The routine use of medication-based interventions
to treat delirium, other than treatments to reduce the agitation that sometimes accompanies
it, are not recommended (5, 6). The routine use of scheduled haloperidol to treat delirium is
not currently recommended given a lack of current evidence regarding its ability to resolve
delirium and its symptoms, nor improve relevant short and longer-term outcomes.

90 At the time this protocol was finalized, two randomized, placebo-controlled trials had 91 evaluated haloperidol for ICU delirium prophylaxis or treatment and found haloperidol use did 92 not affect days spent with delirium, days of mechanical ventilation, nor time spent in the ICU 93 or hospital (7, 8). In one of these randomized controlled trials (RCTs), haloperidol use was 94 associated with less agitation (7). Importantly, both studies were small (a combined total of 95 212 patients were enrolled), the ABCDEF bundle (a multimodal ICU bundle shown to reduce 96 delirium by 50%)(9) was not routinely used, the effect of haloperidol on delirium-related 97 symptoms was not evaluated, and the post-ICU, longer-term outcomes were not considered. 98 Whether the response to haloperidol was different between patients with hyperactive versus 99 hypoactive delirium was also not evaluated. The impact of haloperidol on patients'- and 100 families' experiences with delirium after ICU discharge remains unknown. Whether long-term 101 mortality is causally related to delirium or simply the persistent cognitive and functional 102 decline associated with critical illness can only be established through a randomised trial 103 (10). Moreover, the use of haloperidol in critically ill adults is not without potential safety 104 concerns given it may prolong the QTc interval, induce extrapyramidal effects and cause 105 oversedation. Despite haloperidol's lack of proven efficacy and the safety concerns 106 associated with its use, haloperidol continues to be widely used in ICUs to treat of delirium 107 (11).

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108 In light of the above evidence gaps that were identified at the time this trial was
109 conceptualized, there is a clear need for a large, multi-center, randomised controlled trial to
110 better define the efficacy and safety of haloperidol to treat delirium in critically ill adults. This
111 report describes the protocol for a large, multicentre, randomized, placebo-controlled,

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2 3	112	haloperidol delirium trial that recently started enrolling patients across multiple ICUs in the
4 5 7 8 9 10	113	Netherlands.
	114	
	115	METHODS AND ANALYSIS
11 12	116	Study design
13 14	117	Randomized, double-blind, placebo-controlled trial of haloperidol for the treatment of delirium
15 16 17 18 19 20 21 22 23 24 25 26 27 28 29	118	in patients admitted to one of six participating ICUs in the Rotterdam area in the Netherlands.
	119	See Appendix 1 for the participating hospitals.
	120	
	121	Study population
	122	Consecutive adults admitted to one of the participating ICUs.
	123	
	124	Eligibility criteria
30 31	125	Inclusion criteria for eligibility:
32 33	126	1. Age ≥ 18 years
34 35	127	2. Admitted to the ICU.
36 37	128	Exclusion criteria for eligibility:
30 39 40	129	1. Admitted to the ICU with an acute neurological diagnosis (including acute stroke,
40 41 42	130	traumatic brain injury, intracranial malignancy, anoxic coma). Prior non-acute stroke
43 44	131	or another neurological condition without cognitive deterioration is not an exclusion
45 46	132	criterion.
47 48	133	2. Pregnancy or lactation
49 50	134	3. History of ventricular arrhythmia including "torsade de pointes" (TdP)
51 52	135	4. Known allergy to haloperidol
53 54	136	5. History of dementia or an Informant Questionnaire on Cognitive Decline in the Elderly
55 56 57	137	(IQCODE) score \geq 4 (12)
57 58 59	138	6. History of malignant neuroleptic syndrome or parkinsonism (either Parkinson's
60	139	disease or another hypokinetic rigid syndrome)

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1 2				
2 3 4	140	7. Schizophrer	nia or other psychotic disorder	
5 6 7 8 9 10 11 12 13 14 15 16	141	8. Inability to c	onduct valid delirium screening assessment (e.g. coma, deaf, blind) or	
	142	inability to s	peak the Dutch language	
	143	9. Expected to	die within 24 hours or leave the ICU within 24 hours	
	144			
	145	Inclusion criteria for	randomisation:	
	146	1. Delirium, as	assessed with the Intensive Care Delirium Screening Checklist (ICDSC \geq	
17 18	147	4) or the Co	nfusion Assessment Method for the ICU (positive CAM-ICU assessment),	
19 20 21	148	at the time o	of ICU admission or any ICU day after ICU admission.	
21 22 23 24 25 26 27 28 29 30 31 32 33 24	149	2. Written infor	med consent obtained from the patient or their legal representative	
	150	3. All eligibility	inclusion criteria (from above) are still met.	
	151	Exclusion criteria for randomisation:		
	152	1. Prolonged C	QT-interval (QTc > 500ms)	
	153	2. (recent) "To	rsade de pointes" (TdP)	
	154	3. (recent) Mal	ignant neuroleptic syndrome or parkinsonism	
34 35	155	4. Evidence of	acute alcohol (or substance) withdrawal requiring pharmacological	
 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 	156	intervention	(e.g. benzodiazepines or alfa-2 agonist) to treat	
	157	5. The patient	is expected to die within 24 hours or expected to leave the ICU within 24	
	158	hours.		
	159	6. No (previous	sly) signed informed consent by patient or representative	
	160	7. Current part	icipation in another intervention trial that is evaluating a medication,	
	161	device or be	havioural intervention	
	162			
51 52	163	Study endpoints		
53 54	164	Main study endpoin	<u>t:</u>	
55 56 57	165	ICU delirium- and c	oma free days (DCFDs) (up to 14 days after randomisation).	
57 58 59	166			
60	167	Secondary study er	ndpoints:	
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2 3	168	ICU stay		
4 5 6 7 8 9 10	169	• Demographics: age, sex, admission diagnosis category, APACHE II and APACHE IV,		
	170	SOFA, ICU days before study entry, pre-admission delirium duration in participants		
	171	with delirium on admission.		
11 12	172	Richmond Agitation Sedation Scores (RASS)		
13 14	173	Maximum ICU Mobility Scale (IMS (13)) and day of max IMS.		
15 16 17	174	Quality of sleep (Richards-Campbell Sleep Questionnaire [RCSQ] (14) and with a		
17 18 19	175	visual analogue scale between 1-7 assessing the sleep quality according to the		
19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42	176	nurse).		
	177	Use of "escape medication" for hallucinations and/or agitation (including atypical		
	178	antipsychotics, alpha-2 agonists, GABA-agonists, opiates and "open-label"		
	179	haloperidol).		
	180	 Daily study drug dose corrected for body weight (mg/kg). 		
	181	Auto-extubation rate, removal of invasive devices (intravenous/-arterial catheters,		
	182	drains and tubes).		
	183	Adverse drug associated events (prolonged QTc by EKG, muscle rigidity and other		
	184	associated movements disorders [Simpson Angus Scale (15)] and ventricular		
	185	arrhythmia's including torsade de pointes).		
	186	Blood pressure will be recorded previous to and 1 hour after the first study drug dose		
43 44 45	187	(2.5mg equivalent) and 1 hour after the first 5mg equivalent.		
45 46 47	188	Daily respiratory status (regarding endotracheal intubation and mechanical		
47 48 49 50 51	189	ventilation)		
	190	Time from randomisation to first resolution of delirium		
52 53	191	Time to "readiness for discharge from the ICU"		
54 55 56 57 58 59 60	192	Hospital discharge		

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2		
3 4	193	Patient and family-member well-being and experiences associated with delirium
5 6	194	during and after ICU stay with the ICU Memory Tool (ICU-MT (16)) and Delirium
7 8	195	Experience Questionnaire (DEQ (17)).
9 10	196	28 days after randomization
11 12	197	Mortality rate
13 14	198	3 months after randomization
15 16 17	199	Cognitive outcomes with a brief cognitive assessment battery of validated and
17 18 10	200	repeatable measures of general cognition, memory, language, processing speed,
20 21	201	attention and executive functioning and mood (Montreal Cognitive Assessment
22 23	202	[MOCA](18), Rey Auditory Verbal Learning Test(19), Semantic fluency(20), Digit
24 25	203	Span [WAIS-IV](21), Trail making tests A and B(22), Boston naming Test [short
26 27	204	version](23), Hospital Anxiety and Depression Scale [HADS](24)).
28 29	205	 Functional outcomes and quality of life (Short Form-36 [SF-36](25)).
30 31	206	Patient and family-member well-being and experiences associated with delirium
32 33	207	during and after ICU stay with the ICU Memory Tool (ICU-MT (16)), Delirium
34 35 26	208	Experience Questionnaire (DEQ (17)) and Caregiver Strain Index (CSI (26)).
30 37 38	209	• Posttraumatic stress syndrome (PTSS) in participants and family-members with the
39 40	210	Impact of Event Scale – Revisited (IES-R)(27).
41 42	211	12 months after randomization
43 44	212	Cognitive outcomes with a brief cognitive assessment battery of validated and
45 46	213	repeatable measures of general cognition, memory, language, processing speed,
47 48	214	attention and executive functioning and mood (Montreal Cognitive Assessment
49 50	215	[MOCA](18), Rey Auditory Verbal Learning Test(19), Semantic fluency(20), Digit
51 52	216	Span [WAIS-IV](21), Trail making tests A and B(22), Boston naming Test [short
53 54 55	217	version](23), Hospital Anxiety and Depression Scale [HADS](24)).
56 57	218	• Functional outcomes and quality of life (Short Form-36 [SF-36](25)).
58 59	219	Mortality rate
60		

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3 4 5 6	220	
	221	A cost-effectiveness analysis will be performed in collaboration with the Department of
7 8	222	Health Policy and Management of Erasmus University Rotterdam (see Appendix 2 for more
9 10	223	detailed explanation). The tools for the secondary outcomes are mentioned in Table 1 with
11 12	224	overview of timing of assessments.
13 14 15	225	
15 16	226	Treatment of subjects
17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39	227	Investigational product:
	228	Name: Haldol (haloperidol)
	229	Mechanism: butyrophenone-derived anti-psychotic with mainly dopamine-2 receptor
	230	antagonistic properties
	231	Placebo consists of sodium chloride for injection. Medical staff, patients and family will be
	232	blinded to the product containing haloperidol/placebo.
	233	
	234	Summary of findings from clinical studies and of known and potential risks and benefits:
	235	See: Summary of Product Characteristics (SPC) in Appendix 3 and Systematic Review
	236	(Appendix 4).
	237	
40 41 42	238	Dosages, dosage modifications and method of administration:
42 43 44	239	The following dosing scheme will be used: start with haloperidol/placebo (further called:
45 46	240	"study drug") 2.5mg IV q8h (because of delirium screening once every 8-hour shift) and
47 48	241	increase to a maximum dose of 5mg IV q8h when delirium persists beyond the next 8-hour
49 50	242	shift. Doses will be reduced (50% of dose) in the very old elderly (age \ge 80 years). The study
51 52	243	drug dose will be decreased (when dosage is 5mg IV q8h) or stopped (when dose is 2.5mg
53 54	244	IV q8h) when delirium has resolved for the next 24 hours. Dosages can be lowered also at
55 56	245	the discretion of the treating physician in case of evident rigidity, which is in line with current
57 58 50	246	routine practice. Standard clinical practice for the administration of haloperidol will be
60	247	followed.

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2 3 4	248	
5 6	249	Description and justification of route of administration and dosage:
7 8	250	Administration of the study intervention via the IV (versus the oral or enteral) route is the
9 10	251	most feasible in critically ill patients – a population where gastrointestinal dysfunction is
11 12	252	prevalent and haloperidol absorption (i.e., bioavailability) could be compromised. The dose of
13 14	253	haloperidol or placebo equivalent to be used in the study is based on the following
15 16	254	consideration: 1. PK/PD; 2. Efficacy and 3. Safety. A (pilot) study in Erasmus Medical Center
17 18	255	(n=14 critically ill patients, abstract presented at European Society of Intensive Care
19 20	256	Medicine 2016) showed no adverse events (e.g. no QTc > 500ms), low serum levels (1.5-
21 22 23	257	2.2µg/L) and no clear relation between serum level and delirium resolution with haloperidol
23 24 25	258	dosages up to 2mg IV q8h (or: 3 x 2mg IV). A feasibility trial of haloperidol for ICU delirium
26 27	259	(MIND-trial (8)) that used an average total daily dosage of 15 mg orally found higher serum
28 29	260	levels (interquartile range 2.85-5.8 μ g/L). No differences were found in QTc prolongation
30 31	261	between treatment groups and placebo in this trial. None of these trials demonstrated
32 33	262	clinically important safety concerns associated with haloperidol administration. Finally, a
34 35	263	recently published trial of haloperidol for ICU delirium using haloperidol/placebo 10mg IV
36 37	264	q12h, did not report any safety issues, using a QTc cut-off for safety of 550ms, which may be
38 39 40	265	regarded an indirect signal that such dosages are feasible and safe (28). The maximum dose
40 41 42	266	of haloperidol of up to 5mg IV q8h was further chosen because a previous Dutch guideline
43 44	267	advocating the use of haloperidol recommended an IV haloperidol treatment dose of up to 20
45 46	268	mg/24h period (29). In our protocol, we chose q8h dosing (titrated up to 15mg daily) given
47 48	269	the greater potential susceptibility of critically ill adults to the side effects of haloperidol, and
49 50	270	the fact that this dosage is in line with existing haloperidol delirium protocols in several of the
51 52	271	participating ICUs.
53 54	272	
55 56	273	Patient assessments:
57 58	274	Rigidity will be monitored with the Simpson-Angus scale (15) and the Barnes Akathisia

59 Rating Scale (30) (see "Secondary study endpoints") for study purposes only. The QTc 275

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interval will be measured daily before the administration of the second daily (afternoon) dose using a 12-lead EKG. When the QTc interval is found to be prolonged (> 500ms or an increase from baseline (=at randomisation) of \geq 60ms (31, 32)), all non-study medications having the potential to prolong the QTc will be held if clinically feasible. A Standard Operating Procedure (S.O.P.) lists the drugs known to prolong the QTc. Eight hours later, if QTc prolongation persists, study medication will be held or tapered according to the S.O.P. and only resumed when the EKGs (evaluation frequency increased to q8h in this situation) reveal QTc prolongation to have dissipated. General medical management at participating ICUs: In the six original participating ICUs, institutional delirium guidelines, based on the 2013 PAD guidelines and a Dutch ICU delirium guideline, were rigorously implemented over a three-year period (2012 to 2015) (6, 33, 34). During the inclusion period of the current trial, spot-checks will be performed by members of the investigative team at each center to confirm delirium screening accuracy. Preparation and labelling of Investigational Medicinal Product: Preparation and labelling will be done by the trial pharmacist ("Apotheek A15") according to GMP guidelines. Apotheek A15 is certified for these procedures. Trial medication will be dispensed to the pharmacies of the trial sites by the Hospital Pharmacy of Erasmus MC. See Appendix 5 for a description of the drug accountability. Escape medication: Knowing that half the subjects will be administered placebo, we anticipate two issues may affect the clinical management of enrolled patients: 1) agitation and 2) hallucinations. Agitation management will be based on the following principles: a) treat pain first with opioids; b) use alpha-2 agonist for agitation that either persists or is not caused by pain; c) GABA agonists (e.g. benzodiazepines or propofol) are discouraged, but can be used on a

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3 4	304	short-term basis for the treatment of severe agitation (RASS \geq 2) that cannot be effectively					
5	305	managed by other means.					
7 8	306	Hallucination management will be based on the following principles: a)					
9 10	307	pharmacological treatment may be withheld if the patient indicates they are not in distress; b)	•				
11 12	308	for a patient in distress, a low-dose atypical antipsychotic (e.g., quetiapine 12.5mg q8h) may					
13 14	309	be administered on a short-term basis until the distress resolves.					
15 16	310	Because of the pragmatic design of this trial, within these boundaries, the treatment					
17 18	311	and dose of escape medication is left to the treating physician, since these are part of routine					
19 20	312	practice. However, before start of randomisation these management principles for agitation					
21 22	313	and hallucination will be thoroughly implemented first with the help of detailed S.O.P.'s to					
23 24 25	314	enhance uniformity in participating centres. Adherence to escape medication regimens will					
25 26 27	315	be closely monitored. Open-label haloperidol administration is strongly discouraged during					
27 28 29	316	the trial but can be used if the ICU team considers it necessary for acute breakthrough	л 5				
30 31	317	delirium symptoms that cannot be managed within the management boundaries outlined) 				
32 33	318	above. Open-label haloperidol will be documented.	らううちの				
34 35	319	and					
36 37	320	Randomisation, blinding and treatment allocation	···· / N				
38 39	321	Legal representatives of eligible patients (when the patient is sedated or otherwise	リロのノ				
40 41	322	temporarily unable to consent) or the patient him-/herself will be asked for informed consent	•				
42 43	323	shortly after admission when the patient has no delirium, or as soon as possible after					
44 45	324	admission when the patient already has delirium. In this study the presence of delirium will					
46 47 49	325	be considered to be confirmed when the beside nurse deemed the patient to have delirium $\frac{\overline{a}}{\underline{a}}$.					
40 49 50	326	based on assessment with the ICDSC or CAM-ICU, given the previous large-scale					
50 51 52	327	implementation project (33).					
53 54	328	تة Delirious patients who fulfil all inclusion but no exclusion criteria, and for whom written					
55 56	329	informed consent has been obtained (as recorded in medical file), will be randomised.	(
57 58	330	Randomisation coordination and start of a new Case Record Form (CRF) will be guided by					
59 60	331	the Electronic Data Capture (EDC) system of ALEA, constructed by the Clinical Trial Center	(
		12	•				

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> (CTC) of the Erasmus Medical Center and calibrated with the coordinating (Erasmus MC) and local pharmacies. We will randomise the recruited patients using a block design of 8 patients in one block, and one block is assigned to a center. We will have 8 batches (numbered 1 through 8) of treatment and placebo, with 4 batches of placebo and 4 treatment (haloperidol). Each block will have a random assignment of 8 batch numbers, having four placebo and four haloperidol patients included (a combination of 1 to 4 and 5 to 8 in random order). After 8 patients are included in the study (i.e., a block is full), a new block will be assigned to a center.

Blinding of the medication will be performed by the pharmacy, based on a randomisation list that will be generated electronically through a randomisation module in the EDC system of ALEA. Randomisation will be stratified per study center (i.e. equal number of patients in both study groups, see "statistical analysis" paragraph). Only the involved pharmacists and the trial statistician are aware of the contents of each medication kit, so they can unblind a patient in case of an emergency. Except for the hospital's pharmacist responsible for the randomisation list, all other involved personnel with the study, caregivers, patients or their representatives will remain unaware of the treatment groups until the time of Database Lock. The Unblinding procedure is specified in Appendix 6. Follow-up procedures will be performed according to designated S.O.P.'s. When possible and preferred by patients or families, questionnaires will be sent or visits planned at home when possible, e.g. for incapacitated participants. Withdrawal of individual subjects Subjects can leave the study at any time for any reason if they wish to do so without any

consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

Follow-up of subjects withdrawn from treatment

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2 3	359	Data of withdrawn patients will remain in the database for statistical analysis purposes but
4 5 6 7	360	will not be subject to follow-up. When patients specifically withdraw their consent for usage of
	361	their data, these data will be removed from the database and excluded from all analyses.
8 9 10	362	
11 12	363	Premature termination of the study
13 14	364	The sponsor may decide to terminate the study prematurely based on the following criteria:
15 16 17 18	365	• There is evidence of an unacceptable risk for study patients (i.e. safety issue)
	366	There is reason to conclude that continuation of the study cannot serve a scientific
19 20 21	367	purpose following confirmation of the Data Safety Monitoring Board (DSMB)
21 22 23	368	The DSMB recommends to end the trial based on viable arguments other than
25 24 25	369	described above.
26 27	370	
28 29	371	The following stopping rules have been determined by the DSMB and have been laid down
30 31 32 33 34 35 36	372	in a DSMB charter:
	373	• Early stopping of one individual participant, for example, to clear benefit or harm of a
	374	treatment or the occurrence of serious adverse reactions or events in one patient. In
37 38	375	this case de-blinding of this single patient may be necessary.
39 40	376	• Stopping of the trial as a whole to clear benefit or harm of a treatment or the
41 42	377	occurrence of serious adverse reactions or events. As a result, further patient
43 44	378	enrolment will be stopped. Deblinding may be necessary for all patients.
45 46	379	
47 48 40	380	Reasons to stop the study include:
49 50 51	381	Advice to do so from DSMB
52 53	382	Interim analysis shows a significant benefit difference between the treatment groups
54 55	383	which will not be expected to change after inclusion of all subject as per the power
56 57	384	analysis.
58 59	385	
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86 SUSAR's are not expected due to the vast experience in clinical practice with the study drug 87 (haloperidol). 88

89 If the study is terminated the Medical Ethics Committees of all participating hospital and the 90 CCMO will be notified.

- 92 Safety reporting
- 93 AEs, SAEs and SUSARs:
- 94 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the 95 96 study, whether or not considered related to the investigational product. Since patients 97 admitted to an ICU are critically ill and present with many AEs, only possible adverse drug 98 related events (on days of study drug administration: prolonged QTc by EKG, muscle rigidity 99 and associated movements disorders [Simpson Angus Scale]) as indicated by the subject or 00 observed by the investigator or his staff occurring from the date of randomisation until 14 01 days later or discharge from ICU or death (whichever comes first), will be recorded in the 02 CRF. In addition, the following AEs will be assessed daily during 14 days after 03 randomisation: epilepsy, tachycardia, hypotension (not explained otherwise), hepatic 04 dysfunction (not explained otherwise), leucopenia (not explained otherwise), bronchospasms 05 (not explained otherwise). 06 07 Serious adverse events (SAEs)

08 A SAE is any untoward medical occurrence or effect, occurring during the 14-day study 09 period at the ICU, that (the SAEs for the purpose of the study are shown in *Italics* per item)

10 results in death:

0

- death will always be reported as an SAE 0
- 12 is life threatening (at the time of the event);
- 13

15

ventricular arrhythmia or malignant neuroleptic syndrome

1 2		
3 4	414	 requires hospitalisation or prolongation of existing inpatients' hospitalisation;
5 6	415	• Not to be expected; only applicable when the site investigator is able to
7 8	416	explicitly show a relationship
9 10	417	 results in persistent or significant disability or incapacity;
11 12	418	• Not to be expected; only applicable when the site investigator is able to
13 14 15 16	419	explicitly show a relationship
	420	• is a congenital anomaly or birth defect; (<i>N/A</i>) or
17 18 19	421	any other important medical event that did not result in any of the outcomes listed
20 21	422	above due to medical or surgical intervention but could have been based upon
22 23	423	appropriate judgement by the investigator.
24 25	424	
26 27	425	Statistical analysis
28 29	426	Primary and secondary study parameter(s):
30 31 32 33 34 35 36	427	Statistical analysis will be done according to intention-to-treat-principle. All randomised
	428	participants will be included. The primary outcome is DCFDs, defined as the number of days
	429	in the first 14 days after randomisation during which the patient is alive without delirium and
37 38	430	not in coma from any cause (7). Differences between DCFDs between the haloperidol group
39 40	431	and placebo group will be analyzed using Poisson regression analysis, with adjustment for
41 42	432	differences in baseline characteristics between treatment groups (when present) and for the
43 44	433	different centers. For cognitive and functional outcomes assessed with designated test-
45 46	434	batteries, non-parametric or parametric tests will be used depending on normality of scaled
47 48	435	test-results. Mortality risk will be assessed as a binary end-point. A more detailed statistical
49 50	436	analysis plan, to be drawn up before Data Base Lock, will be drafted for publication
51 52	437	separately.
55 55	438	
56 57	439	Interim analysis:
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> Pre-planned interim analyses will be performed at 1/3 and 2/3 of the trial's course (first analysis ideally estimated at 6 months after start of trial), as determined by the DSMB charter or otherwise when the DSMB requests it. Sample size calculation To achieve statistically significant results with (p<.05) with a power of 90% and a true treatment difference of one day for the primary outcome (from 3.2 DCFDs in the placebo group to 4.2 in the haloperidol group, SD in both groups is equal to 4.2), 371 patients are needed in each group (n=742). These estimates are derived from the previous implementation study, which included 4727 patients in three 4-month periods in the same six participating ICUs and found delirium incidence of 27% (and increase of DCFDs from 60% to 70%)(33). Consequently, presuming an informed consent rate of 40%, we need 18-months to encounter 1900 patients with a newly diagnosed delirium to include the required 742 patients. Because of estimated work-load due to follow-up visits, including e.g. neurocognitive testing, we propose to select a convenience sample of 2/3 of ICU survivors (estimated around 400 of 575 survivors) as a random sample for the cognitive, functional and secondary outcome variables. **Patient and Public Involvement** During the design and conduct of the study we involved two ex-ICU patients as patient-perspective representatives. The primary research question, its outcome measures, and the burden of the intervention have been assessed and found relevant by these patient-representatives. The role and tasks of the patient-representatives for the study have been detailed as: 1) to help select meaningful assessment-tools of patient and family experiences during and after ICU stay, 2) act as liaison between the study management team and the Dutch foundation "Family and patient Centered Intensive Care" (FCIC; one representative is a formal representative for FCIC), 3) act as members of the Stakeholders group to provide

467 advice on the study contents, execution and course at on a regular basis to ensure the

2		
3 4	468	patient and family perspective, 4) advise on the contents of the Patient Information Form
5 6	469	(PIF) and the informed consent procedure, 5) advise on ways to minimise loss to follow-up
7 8	470	for the functional and cognitive outcome assessments, 6) advise on contents and
9 10	471	organisation of symposia during the study on delirium and its consequences with the aim to
11 12	472	better inform participants of the study and their family members and maximize their
13 14	473	involvement, 7) advise on the contents of the supporting website of the trial. Study
15 16	474	participants will be informed about the most important results of the trial, either by post or
17 18	475	symposium, when they indicate this on the informed consent letter.
19 20	476	
21 22 22	477	ETHICS AND DISSEMINATION
23 24 25	478	The study has been approved by the Medical Ethics Committee of the Erasmus University
25 26 27	479	Medical Centre Rotterdam (MEC2017-511) and the Institutional Review Boards of
28 29	480	participating sites. The study will be conducted according to the principles of the Declaration
30 31	481	of Helsinki (version, date, see for the most recent version: www.wma.net) and in accordance
32 33	482	with the Medical Research Involving Human Subjects Act (WMO) and other guidelines,
34 35	483	regulations and Acts.
36 37	484	
38 39	485	Recruitment and consent
40 41	486	Recruitment of eligible patients will be done upon admission. Informed consent for possible
42 43	487	participation (i.e. only when participants develop delirium at the ICU) will be obtained from
44 45 46	488	subjects who are not expected to leave the ICU within the first 24 hours after admission and
47 48	489	are not yet delirious. The informed consent will be obtained from the patient or (if the patient
49 50	490	is unable to consent) from patient's representative. This procedure of prior request for
51 52	491	informed consent will facilitate randomisation when the patient indeed develops delirium,
53 54	492	because randomisation can then be performed 24/7 since informed consent is already
55 56	493	obtained and delirium often surfaces during the evening and night when obtaining informed
57 58	494	consent is difficult. The informed consent procedure will be clearly delineated from the
59 60	495	randomisation procedure. Importantly, when a patient with prior informed consent develops

delirium and can thus be randomised, still a pre-randomisation check with regard to in- and

exclusion criteria will be performed to confirm that the patient fulfils the inclusion, and not the

ICU nurses and physicians (local PI, PhD student, PI, post-doc) will be trained to perform the

exclusion criteria (because this may change over time). A team of dedicated research and

informed consent procedures and help with the randomisations. Moreover, a 24/7 study

consultation telephone number will be opened to help with problems or question during the

study. A second type of randomisation concerns patients who are delirious upon admission

to ICU. These patients' next-of-kin will be asked to grant permission to participate by means

of informed consent when they are legally representative for the patients and the patient has

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597 AUTHORS' CONTRIBUTIONS

598 MJ developed the study protocol, edited and approved the final version, and was responsible

599 for funding and supervising the study coordination. ZT contributed to the protocol

600 development and study implementation. LS is responsible for study coordination. WR

- 5 601 assisted with statistical analysis and NH assisted with pharmacological coordination. RO, AS,
- 7 602 HP and JD were involved in the study design and protocol development. All authors
- 9 603 contributed to the development and refinement of this study protocol. They have read and

604 approved the final version of the protocol.

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All involved local principal investigators (MB, AB, BM, JL, EK, FS, KS) and research nurses
(EB, AB, DD, HE, DG, PO, NR, AV, MC, ET, EH, TZ) have facilitated visits at their site, will
be involved in executing the protocol at their sites and will be responsible for patient
recruitment and data collection in their hospitals, along with follow up of study patients.

1 2		
3 4 5 6 7 8	618	
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53 54	642	
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3 ∡	646 the design of this study and will not have any role during its execution, analyses,						
5	647	interpretati	ion of the data, or decision to submit results.				
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8 9	649	COMPETI	NG INTERESTS STATEMENT				
10 11	040						
12	650	The author	rs declare that they have no competing interests.				
13	651						
15 16	652		BBREVIATIONS				
17 18		ABR	ABR form, General Assessment and Registration form, is the application				
19 20			form that is required for submission to the accredited Ethics Committee (
21			Dutch, ABR = Algemene Beoordeling en Registratie)				
22 23		AE	Adverse Event				
24		AR	Adverse Reaction				
25 26		СА	Competent Authority				
27		CAM-ICU	Confusion Assessment Method for the ICU				
28 29		ССМО	Central Committee on Research Involving Human Subjects; in Dutch:				
30 31			Centrale Commissie Mensgebonden Onderzoek				
32		cv	Curriculum Vitae				
33 34		DSMB	Data Safety Monitoring Board				
35		EU	European Union				
36 37		EudraCT	European drug regulatory affairs Clinical Trials				
38 30		EKG	Electrocardiography				
40		GCP	Good Clinical Practice				
41 42		IB	Investigator's Brochure				
43 44		IC	Informed Consent				
45		ICDSC	Intensive Care Delirium Screening Checklist				
46 47		ICU	Intensive Care Unit				
48		IMP	Investigational Medicinal Product				
49 50		IMPD	Investigational Medicinal Product Dossier				
51 52		METC	Medical research ethics committee (MREC); in Dutch: medisch ethische				
53			toetsing commissie (METC)				
54 55		PAD	Pain, agitation and delirium				
56		RCT	Randomized Controlled Trial				
57 58		(S)AE	(Serious) Adverse Event				
59		S.O.P.	Standard Operating Procedure				
00							

	SPC	Summary of Product Characteristics (in Dutch: officiële productinfomatie					
		IB1-tekst)					
	Sponsor	The sponsor is the	he party that co	mmissions	the organisation o	r performance	
		of the research, f	for example a p	harmaceutic	al		
		company, acadei	mic hospital, so	cientific orga	inisation or investi	gator. A party	
		that provides fun	iding for a stud	y but does n	ot commission it i	s not	
		regarded as the s	sponsor, but re	ferred to as	a subsidising part	y .	
	SUSAR	Suspected Unex	pected Serious	Adverse Re	action		
	TdP	Torsade de Point	tes				
	Wbp	Personal Data Pr	otection Act (ir	n Dutch: Wet	Bescherming Per	soonsgevens)	
	WMO	Medical Research	h Involving Hu	nan Subject	s Act (in Dutch: We	et Medisch-	
		wetenschappelijl	k Onderzoek m	et Mensen)			
653							
654	Table 1. C	verview of timing	of assessment	s, including	required time inve	stment per	
655	visit/ques	tionnaire.					
	Moment	Neurocognitive	Patient and	Functional	Cost effectivity	Other	
	(months)	tests	family	outcomes	questionnaires		
			experiences	(SF-36)	(EQ-5D-5L, iMTA		
			(time in min.)	10	MCQ, iMTA PCQ)		
	Enrolment					Informed	
				1		consent,	
					0,	IQCODE-N,	
					2/	pregnancy test	
						(if applicable),	
						EKG.	
	ICU study					CAM-ICU /	
	period (3x	<i>ı</i>				ICDSC, RASS	
	day)						

IMS, RCSQ.

Only when on

medication:

study

ICU study

period

(once

daily)

	-	1	I		1	
						EKG, Simpson
						Angus Scale.
	0		Patient: ICU-			
	(discharge		MT (15) +			
	from		DEQ (15)			
	hospital)		Family: DEQ			
			(2)			
	1				30 min.	
	3	45-60 min.	Patient: IES-R	10 min.	30 min.	
			(5) + ICU-MT			
			(15) + DEQ			
			(15)			
			Family: IES-R			
			(5) + CSI (5) +			
			DEQ (2)			
	6		- C		30 min.	
	12	45-60 min.		10 min.	30 min.	
656	IQCODE-N = In	formant Questionnai	re on Cognitive Dec	l cline in the Elder	rly – Dutch version	
657	EKG = Electroc	ardiography				
58	Neurocognitive	e tests: Montreal Cog	nitive Assessment ((MOCA), Rey Au	ditory Verbal Learning	Test, Semantic
59	fluency, Digit S	Span (WAIS-IV), Trailm	naking tests A and E	3, Boston namin	g Test (short version), H	lospital Anxiety
60	and Depression	n Scale (HADS)				
61	IMS = ICU Mot	pility Scale, measures	mobility during ICU	J admission		
62	RCSQ = Richard	ds-Campbell Sleep Qu	iestionnaire, measu	ires quality of sl	еер	
63	Simpson Angu	Simpson Angus Scale = measures muscle rigidity and other associated movements disorders				
64	ICU-MT= ICU-N	ICU-MT= ICU-Memory Tool, assesses the experience and memories of ICU admission				
65	DEQ= Delirium	Experience Question	inaire, measures ex	periences linke	d to delirium	
666	IES-R = Impact	of Event Scale Revise	d, assesses distress	linked to a trau	umatic experience (i.e. e	experiencing
67	delirium)					
68	CSI = Caregiver	CSI = Caregiver Strain Index, assesses the strain experienced by the caregiver				
	25	25				

2 3	669	SF-36 = Short Form-36, measures the health-related quality of life
4 5 6	670	EQ-5D-5L = assesses the general health status
7	671	iMTA MCQ = instituut Beleid & Management Gezondheidszorg Medical Consumption Questionnaire (health
9 10	672	care use)
10 11 12	673	iMTA PCQ = instituut Beleid & Management Gezondheidszorg Productivity Cost Questionnaire (productivity
13 14	674	costs)
14 15 16 17 18 19 20 21 22 32 42 52 62 72 82 93 01 22 33 43 53 63 73 83 94 142 43 44 546 47 849 51 52 35 45 56 78 960	675 676	With the exception of the neurocognitive tests, all above mentioned tools are questionnaires that can be administered at home. Real life visits only need to be paid in order to perform the neurocognitive tests.

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Erasmus MC Rotterdam

Albert Schweizer Hospital Dordrecht

Maasstad Hospital Rotterdam

IJsselland Hospital Capelle aan den IJssel

Ikazia Hospital Rotterdam

Franciscus Gasthuis Rotterdam

As of July 2019 two additional ICUs have started recruitment:

Jeroen Bosch Hospital, 's-Hertogenbosch

Radboud University Medical Center, Nijmegen

Appendix 2: Economic evaluation

ECONOMIC EVALUATION

General considerations

The primary economic analysis will be a trial-based **cost-utility analysis** from a societal and a healthcare perspective. This analysis will be performed according to the Dutch guidelines (1, 2). The time horizon will be 12 months after randomisation, in order to take all relevant costs and effects regarding the treatment procedure into account. Additionally, a **cost-effectiveness analysis** performed from a societal and health care perspective will be conducted, using delirium-free and coma-free days as outcomes.

If a difference in quality of life is observed at the end of the follow-up period, we will also perform a **model-based extrapolation** of costs and health benefits up to 5 years, exploring the following scenarios: (1) health benefit remain constant after the follow-up period, (2) health benefits are gradually phased out over the course of the modelling time, (3) health benefits are gradually phased out over the modelling time over the first year after follow-up, (4) health benefits abruptly disappear after the follow-up period, but costs remain until the end of the modelling period.

If treatment with haloperidol leads to better health outcomes at higher costs, or if it leads to worse health outcomes and cost savings, incremental cost-utility and incremental cost-effectiveness ratios will be calculated. These express the additional costs per unit of health gain (QALYs, deliriumfree days, coma-free days) or the savings per unit of health forgone. The uncertainty around the estimates will be addressed using bootstrapping for the analysis of costs and effects in the first 12 months, and using probabilistic sensitivity analysis in the extrapolation model.

Cost analysis

Healthcare costs will be calculated based on patient-level data on health-care utilization, which will be collected from hospital databases and questionnaires, to be filled out at regular intervals by patients and/or informal caregivers. Cost categories include medication, screenings, inpatient days, contacts with healthcare providers (GP, outpatient visits, and therapists). The questionnaire will also contain questions about absence from paid work by the patient and informal caregivers.

Costs will be calculated by multiplying resource utilization with the cost per unit of resource. Some unit costs will be taken from the 2016 Dutch Manual for Costing Studies(3), but the costs of inpatient days will be assessed following the micro-costing method, which is based on comprehensive 'bottom-up' analyses of the activities of staff and other resources that are used

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during those days. Medication prices will be based on the official list prices, including value added tax and increased by a standard prescription reimbursement for the pharmacist. The cost of production loss will be calculated according to the Friction Cost Approach.

Patient outcome analysis

The primary outcome measure in the economic evaluation is the difference in QALYs. The secondary effects are the delirium-free and coma-free days after treatment with haloperidol or placebo. As measuring QALYs in adult critically ill patients is not feasible at baseline, it is not possible to estimate the average number of QALYs for each treatment group. However, assuming that there is no difference at randomisation, it is possible to analyse the difference in quality of life at subsequent measurements in a multilevel regression model. This will enable us to calculate a difference in QALYs between the treatment groups over the total follow-up period, using linear intrapolation. HRQoL will be measured on t=1, 3, 6 and 12 months after randomization using the EQ-5D-5L instrument.

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2 3	Appendix 3: Haloperidol SPC
4 5	
6	See this weblink: <u>https://db.cbg-meb.nl/IB-teksten/h03185.pdf</u>
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Appendix 4: (Semi-) structured review of literature on efficacy and adverse events of haloperidol for delirium in adult critically ill patients

1. Haloperidol as a treatment for ICU delirium

Systematic review of randomised placebo-controlled trials assessing haloperidol for treatment of ICU delirium

Method: A biomedical Information Specialist (BIS) of the Erasmus Medical Center library performed a systematic search aimed at controlled studies on haloperidol for ICU delirium combining the subjects: delirium, ICU and haloperidol, or equivalent terms (see: Appendix for details). No distinction was made in the search between treatment or prevention trials.

Review: Since focus of the EuRIDICE study is on a haloperidol versus placebo comparison, the study selection for this summary is also focused on placebo-controlled haloperidol trials for the treatment of ICU delirium. Systematic reviews from the systematic search are used as a crosscheck to confirm completeness or provide additional insights. The search (total of yielded only 1 study. The MIND trial (2010) was a randomised placebo controlled feasibility, efficacy and safety trial of antipsychotics for ICU delirium in adult mechanically ventilated medical and surgical patients (1). It included three treatment arms (haloperidol, n=35; ziprasidone, n=30 and placebo, n=36) and used a well thought out design (excluding demented patients with a validated tool for cognitive dysfunction, using CAM-ICU as a validated screening tool, a clear protocol with regard to QTc prolongation and study drug dosing, measuring extrapyramidal symptoms with a validated scale and with number of days alive without delirium and coma as the primary outcome (indicating total burden of brain dysfunction, since only assessing delirium days may result in increased coma days and less delirium days being regarded as a – false – improvement). The study used oral haloperidol, no clear sedation protocol aimed at light sedation and crossover antipsychotics were allowed but discouraged. No clear differences were found in the three groups with regard to the primary outcome. Mean haloperidol dose was 15 mg a day but QTc prolongation and extrapyramidal symptoms did not differ between treatment groups. Other medications in this small trial did not differ between groups (propofol, opiates, benzodiazepines). It was concluded that a larger trial would be safe and feasible.

Overview of most recent guidelines' statements on haloperidol as treatment for ICU delirium Method: Pubmed search on published guidelines including ICU delirium and containing information on

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haloperidol. Search terms: guideline, delirium, ICU.

Review: Three recent guidelines were retrieved (2-4). In a Danish guideline (2015) no evidence is stated for pharmacological management(2). A German guideline (2015) advocates symptom-based therapy when delirium screening is positive with haloperidol as a first choice in case of delirium associated with psychotic symptoms only. The "Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit" (2013)(3) advocate avoiding 'antipsychotics' when risk of torsades de pointes or is present or either baseline QT prolongation or concomitant QT prolonging medication is used. It states that there is no evidence that haloperidol decrease delirium duration, which was perceived as the most relevant issue to address with regard to haloperidol treatment of ICU delirium.

Cochrane review(s)

Method: Search on Cochrane (http://www.cochranelibrary.com) for reviews with search term: 'delirium', does not elicit any results pertaining to pharmacological treatment of delirium nor haloperidol.

Review: no Cochrane reviews exist on (ICU) delirium and it's pharmacological management.

On-going trials

Method: A search for 'haloperidol' and 'delirium' in the following online trial databases (and including ICU patients); www.trialregister.nl (0 trials); www.clinicaltrials.gov (4 trials).

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Review: Four trials were retrieved from www.clinicaltrials.gov. One trial ('Haloquet') was not a truly placebo controlled trial because haloperidol was allowed ('as needed') in the placebo group and was last updated in 2013 but not published. It consisted of three treatments arms (also quetiapine) and aimed to include a total of 45 patients (and should thus be considered a pilot trial and not an efficacy trial). A second trial enrolled 40 patients and was completed in 2011 but not published. A third trial was a phase-2 safety/efficacy study enrolling 20 patients, last updated in 2007 and not published. The fourth trial ('The modifying the impact of ICU-associated neurological dysfunction-USA [MIND-USA] study') is currently recruiting (last verified May 2016 on September 14th). It is a multi-center double blind placebo-controlled trial aiming to enrol 561 patients in three treatment arms: haloperidol, ziprasidone and placebo, by the same research group that did the MIND trial. It includes cognitive and

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psychological follow-up at 12 months and is estimated to be completed July 2019. Maximum dose of haloperidol amounts to 10 mg IV q12 hours. Trial design is similar to the EuRIDICE trial, except for the patient experiences and perspective, and the fact that only patients on mechanical ventilation or in shock are included (i.e. the sickest ICU patients). The study protocol has not been published in a peerreviewed journal.

2. Haloperidol to prevent ICU delirium

Systematic review of randomised placebo-controlled trials assessing haloperidol for prevention of ICU delirium; including information from guidelines and Cochrane reviews

Method: A biomedical Information Specialist (BIS) of the Erasmus Medical Center library performed a systematic search aimed at controlled studies on haloperidol for ICU delirium combining the subjects: delirium, ICU and haloperidol, or equivalent terms (see: Appendix for details).

Review: the focus of this section is on randomised placebo-controlled prevention trials of haloperidol for ICU delirium. Three trials were retrieved. One trial included post-operative generally non-critically ill patients (5) and was not further considered for this review. The Hope-ICU trial (2013)(6) was a prophylactic study of haloperidol (2.5mg IV q8h, n=71) versus placebo (n=70) in adult mechanically ventilated ICU patients. The primary end-point of delirium (assessed with CAM-ICU) and coma free days did not differ between groups (5 days in both), but there was a 21% crossover rate with haloperidol in the placebo group. Secondary clinical endpoints such as length of stay at ICU or mortality did not differ but the trial was not powered on these outcomes. Another trial (2016)(7) including mechanically ventilated patients (n=68) with 'subsyndromal' delirium (=an Intensive Care Delirium Screening Checklist [ICDSC] score of 1-3 on a scale of 8, where 4 or more is compatible with delirium) used haloperidol 1mg IV q6h but did not find lower rate of progression to full delirium.

3. Haloperidol: adverse events versus treatment effects in the few available trials

The adverse events associated with haloperidol in the three aforementioned (small) trials (one treatment and two prevention trials) did not include QTc prolongation (with a threshold of >500 ms). In the Hope-ICU trial more opiates and sedatives were administered in the placebo-group but alfa-2
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agonists were not clearly protocolled, more agitation was present and 26% versus 11% antipsychotics' use in the placebo group. The subsyndromal delirium trial similarly found more agitation in the placebo group.

4. Healthcare perspective

A cost-effectiveness analysis of the Hope-ICU trial found that delirium increased cognitive dysfunction at 6 months and reduced quality of life, suggestive of potential cost-effectiveness of haloperidol (8).

5. Added value of the EuRIDICE trial

Based on this review of available pertinent literature after a thorough BIS-supported systematic search, the proposed trial in this grant application is expected to have important potential additional value:

The indication of haloperidol for ICU delirium will be delineated more clearly by this trial: does it decrease ICU brain dysfunction, associated long-term cognitive, functional and psychological outcomes? Is the intervention cost-effective? Are adverse events associated with haloperidol indeed concerning or actually negligible? Or: has haloperidol become obsolete, now that alternatives have been incorporated into clinical practice, mainly the atypical antipsychotics and alpha-2 agonists (dexmedetomidine and clonidine)? The EuRIDICE trial has a very strong potential to answers all of these questions.

A similar trial as EuRIDICE in the United States is on-going. However, US-based delirium research may not necessarily translate to European/Dutch settings as has been shown before (9), which justifies performing a second large multicentre clinical trial. Moreover, evidence on the pharmacological treatment of delirium is needed because of the lack of trials to date, and the level of evidence and generalizability of the efficacy findings for haloperidol will increase with a second trial. Third, cost-effectiveness of the intervention will be assessed from a healthcare and societal perspective and family and patient experiences will be investigated as important secondary outcomes. Further, we aim to include all critically ill patients, and not just the sickest, i.e. those on mechanical ventilation or in shock.

Existing guidelines and systematic reviews will have to be adapted on the basis of the results this proposed trial.

Acknowledgements:

Gerdien B. de Jonge (MSc), biomedical information specialist, Medical Library, Erasmus MC, is kindly

acknowledged for her help in assembling the databases for the systematic review.

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Appendix 5: Drug Accountability

The study drug will be obtained from the hospital pharmacy of each participating ICU. The research nurse of each participating ICU will record the number of the box with study drug for each patient in the CRF.

The research nurse of each participating ICU is responsible for retrieving the boxes with study drug. The amount of vials in the boxes will be counted for each patient and will be noted in the CRF. The research nurse will return unused drug to the hospital pharmacy. The hospital pharmacy will destroy the vials with study drug and will also record this (double administration).

The pharmacist or another appropriate individual who is designated should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, problems and irregularities during injection, the maintenance of the blinding, and the return to the pharmacy of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial patients (if applicable). Investigators should maintain records that document adequately that the patients were provided the doses specified by the protocol and reconcile all investigational product(s).

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Appendix 6: Unblinding Procedure

The study treatment will be unblinded after Database Lock. While the safety of patients should always take priority, maintenance of blinding is crucial to the integrity of a double-blind trial. Before this planned unblinding, the blinding for a specific patient should only be broken when information about the patient's protocol treatment is considered necessary to manage Serious Adverse Events (emergency unblinding). Unblinding procedures should preferably be initiated only after consultation of the principal investigator/coordinating investigator or his/her representative. To initiate an emergency unblinding the pharmacy in charge of the randomisation list should be contacted. Breaking the blinding on a patient will be logged and reported to the coordinating Investigator within 24 hours following the unblinding procedure, using the Emergency Unblinding Form. It is considered a major protocol violation, after which the patient goes off protocol treatment (if applicable).

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

<u>#1</u> #2a	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
<u>#1</u> #2a	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
<u>#1</u> #2a	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
<u>#2a</u>		
	Trial identifier and registry name. If not yet registered, name of intended registry	3
<u>#2b</u>	All items from the World Health Organization Trial Registration Data Set	NA
<u>#3</u>	Date and version identifier	2
<u>#4</u>	Sources and types of financial, material, and other support	22
er revi	ew only - http://bmiopen.bmi.com/site/about/guidelines.xhtml	
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1 2 3 4 5	Roles and responsibilities: contributorship	<u>#5a</u>	Names, affiliations, and roles of protocol contributors	1, 20
5 7 8 9 10 11	Roles and responsibilities: sponsor contact information	<u>#5b</u>	Name and contact information for the trial sponsor	1,2
12 13 14 15 16 17 18 19 20 21	Roles and responsibilities: sponsor and funder	<u>#5c</u>	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22
22 23 24 25 26 27 28 29 30	Roles and responsibilities: committees	<u>#5d</u>	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14
31 32	Introduction			
33 34 35 36 37 38 39	Background and rationale	<u>#6a</u>	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-5
40 41 42 43 44	Background and rationale: choice of comparators	<u>#6b</u>	Explanation for choice of comparators	3-5
45 46	Objectives	<u>#7</u>	Specific objectives or hypotheses	4
47 48 49 50 51 52 53	Trial design	<u>#8</u>	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
54 55	Methods:			
57	Participants,			
58 59 60	Fc	or peer revie	ew only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

1 2 3	interventions, and outcomes			
4 5 6 7 8 9 10 11 12 13 14 15 16	Study setting	<u>#9</u>	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
	Eligibility criteria	<u>#10</u>	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-6
17 18 19 20 21	Interventions: description	<u>#11a</u>	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10
22 23 24 25 26 27 28	Interventions: modifications	<u>#11b</u>	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9-12
29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55	Interventions: adherance	<u>#11c</u>	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	11
	Interventions: concomitant care	<u>#11d</u>	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11-12
	Outcomes	<u>#12</u>	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-9
	Participant timeline	<u>#13</u>	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7-9
56 57 58 59 60	Sample size	<u>#14</u> peer revie	Estimated number of participants needed to achieve study objectives and how it was determined, including w only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	17

			BMJ Open	Page 42 of	f 44 oo
1 2			clinical and statistical assumptions supporting any sample size calculations		MJ Open:
3 4 5 6	Recruitment	<u>#15</u>	Strategies for achieving adequate participant enrolment to reach target sample size	12	first publisł
 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 	Methods: Assignment of interventions (for controlled trials)			Protected	hed as 10.1136/bmj
	Allocation: sequence generation	<u>#16a</u>	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	by copyright, including for uses	open-2019-036735 on 23 Septem
	Allocation concealment mechanism	<u>#16b</u>	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12-13 12-13 12-13	iber 2020. Downloa
	Allocation: implementation	<u>#16c</u>	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	data mining, A	ded from http:/
37 38 39 40 41 42	Blinding (masking)	<u>#17a</u>	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12-13 training, and s	/bmjopen.bmj.c
43 44 45 46 47	Blinding (masking): emergency unblinding	<u>#17b</u>	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12-13 lar technok	:om/ on June 9,
48 49 50 51 52 53 54	Methods: Data collection, management, and analysis			ogies.	, 2025 at Agence Bi
55 56 57 58 59 60	Data collection plan	<u>#18a</u> peer revie	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate w only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	7-9	bliographique de l

Page 4	3 of 44		BMJ Open	
1 2 3 4 5 6 7			measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
8 9 10 11 12 13 14	Data collection plan: retention	<u>#18b</u>	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13-14
15 16 17 18 19 20 21 22	Data management	<u>#19</u>	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12, 15
23 24 25 26 27 28 29	Statistics: outcomes	<u>#20a</u>	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16
30 31 32	Statistics: additional analyses	<u>#20b</u>	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16-17
33 34 35 36 37 38 39	Statistics: analysis population and missing data	<u>#20c</u>	Definition of analysis population relating to protocol non- adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
40 41 42	Methods: Monitoring			
43 44 45 46 47 48 49 50 51 52 53	Data monitoring: formal committee	<u>#21a</u>	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
54 55 56 57 58	Data monitoring: interim analysis	<u>#21b</u>	Description of any interim analyses and stopping guidelines, including who will have access to these	16-17
59 60	For	peer revie	w only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

			BMJ Open	Page 4	4 of 44 ص
1 2			interim results and make the final decision to terminate the trial		MJ Open:
3 4 5 6 7 8 9	Harms	<u>#22</u>	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15-16	first published as 1
10 11 12 13 14 15	Auditing	<u>#23</u>	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA	0.1136/bmjoper Protected by c
16	Ethics and			;	1-201 оруг
17 18	dissemination				9-036; ight, ir
19 20 21 22	Research ethics approval	<u>#24</u>	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	17	735 on 23 S 1cluding fo
23 24 25 26 27 28 29 30 31	Protocol amendments	<u>#25</u>	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	17	eptember 2020. Downlc Enseignement Super r uses related to text an
32 33 34 35 36	Consent or assent	<u>#26a</u>	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18	baded from http ieur (ABES) . Id data mining,
37 38 39 40 41	Consent or assent: ancillary studies	<u>#26b</u>	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA	://bmjopen.bmj Al training, and
42 43 44 45 46 47 48	Confidentiality	<u>#27</u>	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18	<mark>j.com/</mark> on June 9, 20 I similar technologie
49 50 51 52	Declaration of interests	<u>#28</u>	Financial and other competing interests for principal investigators for the overall trial and each study site	22)25 at Agei es.
53 54 55 56 57 58 59 60	Data access	<u>#29</u> peer revie	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators w only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	-	nce Bibliographique de

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Ancillary and post trial care	<u>#30</u>	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy: trial results	<u>#31a</u>	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	3
Dissemination policy: authorship	<u>#31b</u>	Authorship eligibility guidelines and any intended use of professional writers	-
issemination policy: eproducible research	<u>#31c</u>	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	<u>#32</u>	Model consent form and other related documentation given to participants and authorised surrogates	-
Biological specimens	<u>#33</u>	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA
None The SPIRIT check License CC-BY-ND 3.0. ool made by the <u>EQUA</u>	klist is di This ch <u>TOR Ne</u>	stributed under the terms of the Creative Commons Attributed ecklist can be completed online using <u>https://www.goodrep</u> etwork in collaboration with <u>Penelope.ai</u>	ion orts.org/
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Efficacy of halopeRIdol to decrease the burden of Delirium In adult Critically ill patiEnts (EuRIDICE): study protocol for a prospective randomised multi-center double-blind placebo-controlled clinical trial

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1	Efficacy of halopeRIdol to decrease the burden of Delirium In adult
2	Critically ill patiEnts (EuRIDICE): study protocol for a prospective
3	randomised multi-center double-blind placebo-controlled clinical
4	trial
5	
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	34	Protocol version: November 16 th 2017, Version 2
15 16	35	
17 18	36	Word count: 4326 words
19 20 21	37	
21 22 23	38	ABSTRACT
24 25	39	Introduction: Delirium in critically ill adults is associated with prolonged hospital stay,
26 27	40	increased mortality and greater cognitive and functional decline. Current practice guideline
28 29 30 31 32 33 34 35 36 37 38 39	41	recommendations advocate the use of non-pharmacologic strategies to reduce delirium. The
	42	routine use of scheduled haloperidol to treat delirium is not recommended given a lack of
	43	evidence regarding its ability to resolve delirium nor improve relevant short and longer-term
	44	outcomes. This study aims to evaluate the efficacy and safety of haloperidol for the treatment
	45	of delirium in adult critically ill patients to reduce days spent with coma or delirium.
	46	Methods and analysis: EuRIDICE is a prospective, multicentre, randomized, double-blind,
40 41 42	47	placebo-controlled, trial. Study population consists of adult ICU patients without acute
43 44	48	neurologic injury who have delirium based on a positive Intensive Care Delirium Screening
45 46	49	Checklist (ICDSC) or Confusion Assessment Method for the ICU (CAM-ICU) assessment.
47 48	50	Intervention is intravenous haloperidol 2.5 mg (or matching placebo) every 8 hours, titrated
49 50	51	daily based on ICDSC or CAM-ICU positivity to a maximum of 5 mg every 8 hours, until
51 52	52	delirium resolution or ICU discharge. Main study endpoint is delirium and coma free days
53 54	53	(DCFD) up to 14 days after randomisation. Secondary endpoints include 1) 28-day and 1-
55 56	54	year mortality; 2) cognitive and functional performance at 3 and 12 months; 3) patient- and
57 58	55	family delirium and ICU experience; 4) psychological sequelae during and after ICU stay; 4)
60	56	safety concerns associated with haloperidol use; and 5) cost-effectiveness. Differences in

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2 3	57	DCEDs between belongridel and placebo group will be applyined using Deisson regression
4 5	57	berbs between halopendol and placebo group will be analysed dsing Poisson regression
6	58	analysis. Study recruitment started in February 2018 and continues.
/ 8	59	Ethics and dissemination: The study has been approved by the Medical Ethics Committee
9 10	60	of the Erasmus University Medical Centre Rotterdam (MEC2017-511). Its results will be
11 12	61	disseminated via peer-reviewed publication and conference presentations.
13 14	62	Trial registration: ClinicalTrials, NCT03628391. Registered 14 August 2018 -
15 16 17	63	https://clinicaltrials.gov/ct2/show/NCT03628391.
17 18 10	64	
20 21	65	Strengths and limitations of this study
22 23	66	- This study is the first European sufficiently powered randomised multi-center
24 25	67	double-blind placebo-controlled clinical trial;
26 27	68	- Extensive neurocognitive testing will be conducted with a valid test battery in
28 29	69	order to assess cognitive impairment at 3 and 12 months after ICU admission;
30 31	70	- We will assess patient- and family experiences associated with delirium as a
32 33	71	novel outcome;
34 35	72	
36 37	73	INTRODUCTION
38 39 40	74	Delirium occurs in up to 80% of patients admitted to the Intensive Care Unit (ICU) (1, 2) and
40 41 42	75	is associated with greater ICU and post-ICU mortality (2). Cognitive dysfunction and
43 44	76	functional decline after critical illness is common, frequently persists for months after ICU
45 46	77	discharge, and is worse among patients who experience delirium (2, 3). The symptoms and
47 48	78	sequelae of delirium, including fear, anxiety, disrupted sleep, and post-traumatic stress
49 50	79	disorder, may persist for months after ICU discharge. The health and societal costs of
51 52	80	delirium are estimated to exceed \$10 billion per year in the USA alone (4).
53 54	81	Given the burden and costs of delirium in critically ill adults, substantial research
55 56	82	efforts have been devoted to identify safe and effective strategies to treat it. Current evidence
57 58	83	and practice guideline recommendations advocate the use of non-pharmacologic strategies
60 60	84	to reduce delirium, including avoidance of benzodiazepine sedation, early mobilization and

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the use of sleep improvement protocols. The routine use of medication-based interventions
to treat delirium, other than treatments to reduce the agitation that sometimes accompanies
it, are not recommended (5, 6). The routine use of scheduled haloperidol to treat delirium is
not currently recommended given a lack of current evidence regarding its ability to resolve
delirium and its symptoms, nor improve relevant short and longer-term outcomes.

90 At the time this protocol was finalized, two randomized, placebo-controlled trials had 91 evaluated haloperidol for ICU delirium prophylaxis or treatment and found haloperidol use did 92 not affect days spent with delirium, days of mechanical ventilation, nor time spent in the ICU 93 or hospital (7, 8). In one of these randomized controlled trials (RCTs), haloperidol use was 94 associated with less agitation (7). Importantly, both studies were small (a combined total of 95 212 patients were enrolled), the ABCDEF bundle (a multimodal ICU bundle shown to reduce 96 delirium by 50%)(9) was not routinely used, the effect of haloperidol on delirium-related 97 symptoms was not evaluated, and the post-ICU, longer-term outcomes were not considered. 98 Whether the response to haloperidol was different between patients with hyperactive versus 99 hypoactive delirium was also not evaluated. The impact of haloperidol on patients'- and 100 families' experiences with delirium after ICU discharge remains unknown. Whether long-term 101 mortality is causally related to delirium or simply the persistent cognitive and functional 102 decline associated with critical illness can only be established through a randomised trial 103 (10). Moreover, the use of haloperidol in critically ill adults is not without potential safety 104 concerns given it may prolong the QTc interval, induce extrapyramidal effects and cause 105 oversedation. Despite haloperidol's lack of proven efficacy and the safety concerns 106 associated with its use, haloperidol continues to be widely used in ICUs to treat of delirium 107 (11).

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108 In light of the above evidence gaps that were identified at the time this trial was
109 conceptualized, there is a clear need for a large, multi-center, randomised controlled trial to
110 better define the efficacy and safety of haloperidol to treat delirium in critically ill adults. This
111 report describes the protocol for a large, multicentre, randomized, placebo-controlled,

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2 3 4 5 6 7 8 9 10	112	haloperidol delirium trial that recently started enrolling patients across multiple ICUs in the
	113	Netherlands.
	114	
	115	METHODS AND ANALYSIS
11 12	116	Study design
13 14	117	Randomized, double-blind, placebo-controlled trial of haloperidol for the treatment of delirium
15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33	118	in patients admitted to one of six participating ICUs in the Rotterdam area in the Netherlands.
	119	See Appendix 1 for the participating hospitals.
	120	
	121	Study population
	122	Consecutive adults admitted to one of the participating ICUs.
	123	
	124	Eligibility criteria
	125	Inclusion criteria for eligibility:
	126	1. Age ≥ 18 years
34 35	127	2. Admitted to the ICU.
36 37 38 39 40 41 42 43 44	128	Exclusion criteria for eligibility:
	129	1. Admitted to the ICU with an acute neurological diagnosis (including acute stroke,
	130	traumatic brain injury, intracranial malignancy, anoxic coma). Prior non-acute stroke
	131	or another neurological condition without cognitive deterioration is not an exclusion
45 46	132	criterion.
47 48	133	2. Pregnancy or lactation
49 50	134	3. History of ventricular arrhythmia including "torsade de pointes" (TdP)
51 52	135	4. Known allergy to haloperidol
53 54	136	5. History of dementia or an Informant Questionnaire on Cognitive Decline in the Elderly
55 56	137	(IQCODE) score \geq 4 (12)
57 58 50	138	6. History of malignant neuroleptic syndrome or parkinsonism (either Parkinson's
60	139	disease or another hypokinetic rigid syndrome)

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1 2			
3 4	140	7. Schizophrenia or other psychot	c disorder
5 6	141	8. Inability to conduct valid deliriur	n screening assessment (e.g. coma, deaf, blind) or
7 8	142	inability to speak the Dutch lang	luage
9 10	143	9. Expected to die within 24 hours	or leave the ICU within 24 hours
11 12	144		
13 14	145	nclusion criteria for randomisation:	
15 16	146	1. Delirium, as assessed with the	ntensive Care Delirium Screening Checklist (ICDSC ≥
17 18	147	4) or the Confusion Assessmen	t Method for the ICU (positive CAM-ICU assessment),
19 20 21	148	at the time of ICU admission or	any ICU day after ICU admission.
21 22 23	149	2. Written informed consent obtair	ed from the patient or their legal representative
23 24 25	150	3. All eligibility inclusion criteria (fr	om above) are still met.
26 27	151	Exclusion criteria for randomisation:	
28 29	152	1. Prolonged QT-interval (QTc > 5	00ms)
30 31	153	2. (recent) "Torsade de pointes" (7	dP)
32 33	154	3. (recent) Neuroleptic malignant	syndrome or parkinsonism
34 35	155	4. Evidence of acute alcohol (or su	ubstance) withdrawal requiring pharmacological
36 37	156	intervention (e.g. benzodiazepir	nes or alpha-2 agonist) to treat
38 39	157	5. The patient is expected to die w	ithin 24 hours or expected to leave the ICU within 24
40 41 42	158	hours.	
42 43 44 45 46 47 48 49 50 51 52	159	6. No (previously) signed informed	consent by patient or representative
	160	7. Current participation in another	intervention trial that is evaluating a medication,
	161	device or behavioural interventi	on
	162		
	163	Study outcomes	
53 54	164	Main study outcome:	
55 56	165	CU delirium- and coma free days (DCI	Ds) (up to 14 days after randomisation).
57 58	166		
59 60	167	Secondary study outcomes:	
		3	

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3 4	168	During ICU stay
5 6	169	Richmond Agitation Sedation Scale (RASS)
7 8	170	• Maximum ICU Mobility Scale (IMS (13)) and day of max IMS.
9 10	171	Quality of sleep (Richards-Campbell Sleep Questionnaire [RCSQ] (14) and with a
11 12 12	172	visual analogue scale between 1-7 assessing the sleep quality according to the
13 14 15	173	nurse).
15 16 17	174	Use of "escape medication" for hallucinations and/or agitation (including atypical
18 19	175	antipsychotics, alpha-2 agonists, GABA-agonists, opiates and "open-label"
20 21	176	haloperidol).
22 23	177	 Daily study drug dose corrected for body weight (mg/kg).
24 25 26 27 28 29 30 31 32	178	• Self-extubation rate, removal of invasive devices (intravenous/-arterial catheters,
	179	drains and tubes).
	180	Adverse drug associated events (prolonged QTc by EKG, muscle rigidity and other
	181	associated movements disorders [Simpson Angus Scale (15)] and ventricular
33 34	182	arrhythmia's including torsade de pointes).
34 35 36	183	• Blood pressure will be recorded previous to and 1 hour after the first study drug dose
37 38	184	(2.5mg equivalent) and 1 hour after the first 5mg equivalent.
39 40	185	Daily respiratory status (regarding endotracheal intubation and mechanical
41 42	186	ventilation)
43 44 45	187	Time from randomisation to first resolution of delirium
43 46 47	188	Time to "readiness for discharge from the ICU"
48 49	189	Hospital discharge
50 51	190	Patient and family-member well-being and experiences associated with delirium
52 53	191	during and after ICU stay with the ICU Memory Tool (ICU-MT (16)) and Delirium
54 55	192	Experience Questionnaire (DEQ (17)).
56 57	193	28 days after randomization
58 59 60	194	Mortality rate

7

2 3 4	195	3 months after randomization
5 6 7 8	196	Cognitive outcomes with a detailed cognitive assessment battery of validated and
	197	repeatable measures of general cognition, memory, language, processing speed,
9 10	198	attention and executive functioning and mood (Montreal Cognitive Assessment
11 12	199	[MOCA](18), Rey Auditory Verbal Learning Test(19), Semantic fluency(20), Digit
13 14	200	Span [WAIS-IV](21), Trail making tests A and B(22), Boston naming Test [short
15 16 17	201	version](23), Hospital Anxiety and Depression Scale [HADS](24)).
17 18 19	202	 Functional outcomes and quality of life (Short Form-36 [SF-36](25)).
20 21	203	Patient and family-member well-being and experiences associated with delirium
22 23	204	during and after ICU stay with the ICU Memory Tool (ICU-MT (16)), Delirium
24 25	205	Experience Questionnaire (DEQ (17)) and Caregiver Strain Index (CSI (26)).
26 27	206	Posttraumatic stress syndrome (PTSS) in participants and family-members with the
28 29 30 31	207	Impact of Event Scale – Revised (IES-R)(27).
	208	12 months after randomization
32 33 34	209	Cognitive outcomes with a detailed cognitive assessment battery of validated and
34 35 36	210	repeatable measures of general cognition, memory, language, processing speed,
37 38	211	attention and executive functioning and mood (Montreal Cognitive Assessment
39 40	212	[MOCA](18), Rey Auditory Verbal Learning Test(19), Semantic fluency(20), Digit
41 42	213	Span [WAIS-IV](21), Trail making tests A and B(22), Boston naming Test [short
43 44	214	version](23), Hospital Anxiety and Depression Scale [HADS](24)).
45 46	215	 Functional outcomes and quality of life (Short Form-36 [SF-36](25)).
47 48	216	Mortality rate
49 50 51	217	
52 53	218	A cost-effectiveness analysis will be performed in collaboration with the Department of
54 55	219	Health Policy and Management of Erasmus University Rotterdam (see Appendix 2 for more
56 57	220	detailed explanation). The tools for the secondary outcomes are mentioned in Table 1 with
58 59 60	221	overview of timing of assessments.

1 2		
3 4 5 6 7	222	
	223	Treatment of subjects
7 8	224	Investigational product:
9 10	225	Name: Haldol (haloperidol)
11 12	226	Mechanism: butyrophenone-derived anti-psychotic with mainly dopamine-2 receptor
13 14	227	antagonistic properties
15 16	228	Placebo consists of sodium chloride for injection. Medical staff, patients and family will be
17 18	229	blinded to the product containing haloperidol/placebo.
19 20 21	230	
21 22 23	231	Summary of findings from clinical studies and of known and potential risks and benefits:
24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44	232	See: Summary of Product Characteristics (SPC) in Appendix 3 and Systematic Review
	233	(Appendix 4).
	234	
	235	Dosages, dosage modifications and method of administration:
	236	The following dosing scheme will be used: start with haloperidol/placebo (further called:
	237	"study drug") 2.5mg IV q8h (because of delirium screening once every 8-hour shift) and
	238	increase to a maximum dose of 5mg IV q8h when delirium persists during the next 8-hour
	239	shift. Doses will be reduced (50% of dose) in the very old elderly (age \geq 80 years). The study
	240	drug dose will be decreased (when dosage is 5mg IV q8h) or stopped (when dose is 2.5mg
	241	IV q8h) when delirium has resolved (or is un-assessable due to coma) for the next 24 hours
45 46	242	(implying: three consecutive delirium assessments during three shifts). Dosages can be
47 48	243	lowered also at the discretion of the treating physician in case of evident rigidity, which is in
49 50	244	line with current routine practice. Standard clinical practice for the administration of
51 52 53 54	245	haloperidol will be followed.
	246	
55 56	247	Description and justification of route of administration and dosage:
57 58	248	Administration of the study intervention via the IV (versus the oral or enteral) route is the
59 60	249	most feasible in critically ill patients – a population where gastrointestinal dysfunction is
		9
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prevalent and haloperidol absorption (i.e., bioavailability) could be compromised. The dose of haloperidol or placebo equivalent to be used in the study is based on the following consideration: 1. PK/PD; 2. Efficacy and 3. Safety. A (pilot) study in Erasmus Medical Center (n=14 critically ill patients, abstract presented at European Society of Intensive Care Medicine 2016) showed no adverse events (e.g. no QTc > 500ms), low serum levels (1.5-2.2µg/L) and no clear relation between serum level and delirium resolution with haloperidol dosages up to 2mg IV q8h (or: 3 x 2mg IV). A feasibility trial of haloperidol for ICU delirium (MIND-trial (8)) that used an average total daily dosage of 15 mg orally found higher serum levels (interguartile range 2.85-5.8 µg/L). No differences were found in QTc prolongation between treatment groups and placebo in this trial. None of these trials demonstrated clinically important safety concerns associated with haloperidol administration. Finally, a recently published trial of haloperidol for ICU delirium using haloperidol/placebo 10mg IV g12h, did not report any safety issues, using a QTc cut-off for safety of 550ms, which may be regarded an indirect signal that such dosages are feasible and safe (28). The maximum dose of haloperidol of up to 5mg IV q8h was further chosen because a previous Dutch guideline advocating the use of haloperidol recommended an IV haloperidol treatment dose of up to 20 mg/24h period (29). In our protocol, we chose g8h dosing (titrated up to 15mg daily) given the greater potential susceptibility of critically ill adults to the side effects of haloperidol, and the fact that this dosage is in line with existing haloperidol delirium protocols in several of the participating ICUs.

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Patient assessments:

Rigidity will be monitored with the Simpson-Angus scale (15) and the Barnes Akathisia Rating Scale (30) (see "Secondary study endpoints") for study purposes only. The QTc interval will be measured daily before the administration of the second daily (afternoon) dose using a 12-lead EKG. When the QTc interval is found to be prolonged (> 500ms or an increase from baseline (=at randomisation) of \geq 60ms (31, 32)), all non-study medications having the potential to prolong the QTc will be held if clinically feasible. A Standard Operating

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2 3	278	Procedure (S.O.P.) lists the drugs known to prolong the QTc. Eight hours later, if QTc
4 5 6 7	279	prolongation persists, study medication will be held or tapered according to the S.O.P. and
	280	only resumed when the EKGs (evaluation frequency increased to q8h in this situation) reveal
o 9 10	281	QTc prolongation to have dissipated.
10 11 12	282	
13 14	283	General medical management at participating ICUs:
15 16	284	In the six original participating ICUs, institutional delirium guidelines, based on the 2013 PAD
17 18	285	guidelines and a Dutch ICU delirium guideline, were rigorously implemented over a three-
19 20	286	year period (2012 to 2015) (6, 33, 34). During the inclusion period of the current trial, spot-
21 22	287	checks will be performed by members of the investigative team at each center to confirm
23 24	288	delirium screening accuracy, as a quality-of-assessments measure and these will be
25 26 27	289	documented in a qualitative manner.
27 28 29	290	
30 31	291	Preparation and labelling of Investigational Medicinal Product:
32 33	292	Preparation and labelling will be done by the trial pharmacist ("Apotheek A15") according to
34 35	293	GMP guidelines. Apotheek A15 is certified for these procedures. Trial medication will be
36 37	294	dispensed to the pharmacies of the trial sites by the Hospital Pharmacy of Erasmus MC. See
38 39	295	Appendix 5 for a description of the drug accountability.
40 41	296	
42 43	297	Escape medication:
44 45 46	298	Knowing that half the subjects will be administered placebo, we anticipate two issues may
47 48	299	affect the clinical management of enrolled patients: 1) agitation and 2) hallucinations.
49 50 51 52	300	Agitation management will be based on the following principles: a) treat pain first with
	301	opioids; b) use alpha-2 agonist for agitation that either persists or is not caused by pain; c)
53 54	302	GABA agonists (e.g. benzodiazepines or propofol) are discouraged, but can be used on a
55 56	303	short-term basis for the treatment of severe agitation (RASS \geq 2) that cannot be effectively
57 58	304	managed by other means.
59 60		

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2 3	305	Hallucination management will be based on the following principles: a)
4 5	306	pharmacological treatment may be withheld if the patient indicates they are not in distress; b)
6 7	307	for a patient in distress, a low-dose atypical antipsychotic (e.g., quetiapine 12.5mg q8h) may
8 9 10	308	be administered on a short-term basis until the distress resolves.
10 11 12	309	Because of the pragmatic design of this trial, within these boundaries, the treatment
13 14	310	and dose of escape medication is left to the treating physician, since these are part of routine
15 16	311	practice. However, before start of randomisation these management principles for agitation
17 18	312	and hallucination will be thoroughly implemented first with the help of detailed S.O.P.'s to
19 20	313	enhance uniformity in participating centres. Adherence to escape medication regimens will
21 22	314	be closely monitored. Open-label haloperidol administration is strongly discouraged during
23 24 25	315	the trial but can be used if the ICU team considers it necessary for acute breakthrough
23 26 27	316	delirium symptoms that cannot be managed within the management boundaries outlined
27 28 29	317	above. Open-label haloperidol will be documented.
30 31	318	
32 33	319	Randomisation, blinding and treatment allocation
 34 35 36 37 38 39 40 41 42 43 44 	320	Legal representatives of eligible patients (when the patient is sedated or otherwise
	321	temporarily unable to consent) or the patient him-/herself will be asked for informed consent
	322	shortly after admission when the patient has no delirium, or as soon as possible after
	323	admission when the patient already has delirium. In this study the presence of delirium will
	324	be considered to be confirmed when the beside nurse deemed the patient to have delirium
45 46	325	based on assessment with the ICDSC or CAM-ICU, given the previous large-scale
47 48	326	implementation project (33).
49 50	327	Delirious patients who fulfil all inclusion but no exclusion criteria, and for whom written
51 52	328	informed consent has been obtained (as recorded in medical file), will be randomised.
53 54	329	Randomisation coordination and start of a new Case Record Form (CRF) will be guided by
55 56 57	330	the Electronic Data Capture (EDC) system of ALEA, constructed by the Clinical Trial Center
58 59	331	(CTC) of the Erasmus Medical Center and calibrated with the coordinating (Erasmus MC)
60	332	and local pharmacies. We will randomise the recruited patients using a block design of 8
		12

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patients in one block, and one block is assigned to a center. We will have 8 batches
(numbered 1 through 8) of treatment and placebo, with 4 batches of placebo and 4 treatment
(haloperidol). Each block will have a random assignment of 8 batch numbers, having four
placebo and four haloperidol patients included (a combination of 1 to 4 and 5 to 8 in random
order). After 8 patients are included in the study (i.e., a block is full), a new block will be
assigned to a center.

Upon randomisation, the study drug with the corresponding randomisation kit number 1-8 (based on 8 medication batches consisting of either haloperidol or placebo) will be obtained from the hospital pharmacy of each participating ICU. Each box from a batch/kit contains 10 ampules (5mg/1ml) of haloperidol or placebo. If all ampules are used, a new box from the same medication kit number with 10 ampules will be used. Study drugs are administered on prescription in the electronic patient data management system (PDMS) and are double-checked by ICU nurses before administration, which is similar to regular practice. Furthermore, the kit number was noted upon randomisation in the medical file and the kit number could be retrieved at any time from the PDMS after first prescription upon randomisation.

Blinding of the medication will be performed by the pharmacy, based on a randomisation list that will be generated electronically through a randomisation module in the EDC system of ALEA. Randomisation will be stratified per study center (i.e. equal number of patients in both study groups, see "statistical analysis" paragraph). Only the involved pharmacists and the trial statistician are aware of the contents of each medication kit. Only the local (site) pharmacists are able to unblind study treatment of a patient in case of an emergency. Except for the hospital's pharmacist responsible for the randomisation list, all other involved personnel with the study, caregivers, patients or their representatives will remain unaware of the treatment groups until the time of Database Lock. The Unblinding procedure is specified in Appendix 6.

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3 4 5 6 7 8	359	Follow-up procedures will be performed according to designated S.O.P.'s. When possible
	360	and preferred by patients or families, questionnaires will be sent or visits planned at home
	361	when possible, e.g. for incapacitated participants.
9 10	362	
11 12	363	Withdrawal of individual subjects
13 14	364	Subjects can leave the study at any time for any reason if they wish to do so without any
15 16 17	365	consequences. The investigator can decide to withdraw a subject from the study for urgent
17 18 10	366	medical reasons.
20 21	367	
22 23	368	Follow-up of subjects withdrawn from treatment
24 25	369	Data of withdrawn patients will remain in the database for statistical analysis purposes but
26 27	370	will not be subject to follow-up. When patients specifically withdraw their consent for usage of
28 29	371	their data, these data will be removed from the database and excluded from all analyses.
30 31	372	
32 33	373	Premature termination of the study
34 35 26	374	The sponsor may decide to terminate the study prematurely based on the following criteria:
30 37 38	375	There is evidence of an unacceptable risk for study patients (i.e. safety issue)
 39 40 41 42 43 44 	376	There is reason to conclude that continuation of the study cannot serve a scientific
	377	purpose following confirmation of the Data Safety Monitoring Board (DSMB)
	378	The DSMB recommends to end the trial based on viable arguments other than
45 46	379	described above.
47 48	380	
49 50	381	The following stopping rules have been determined by the DSMB and have been laid down
51 52	382	in a DSMB charter:
55 55	383	• Early stopping of one individual participant, for example, to clear benefit or harm of a
56 57	384	treatment or the occurrence of serious adverse reactions or events in one patient. In
58 59 60	385	this case de-blinding of this single patient may be necessary.

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3 4	386	 Stopping of the trial as a whole to clear benefit or harm of a treatment or the
5 6 7 8	387	occurrence of serious adverse reactions or events. As a result, further patient
	388	enrolment will be stopped. Deblinding may be necessary for all patients.
9 10	389	
11 12	390	Reasons to stop the study include:
13 14	391	Advice to do so from DSMB
15 16 17	392	Interim analysis shows a significant benefit difference between the treatment groups
17 18 19	393	which will not be expected to change after inclusion of all subject as per the power
20 21	394	analysis.
22 23	395	
24 25	396	SUSAR's are not expected due to the vast experience in clinical practice with the study drug
26 27 28 29	397	(haloperidol).
	398	
30 31	399	If the study is terminated the Medical Ethics Committees of all participating hospital and the
32 33 24	400	CCMO will be notified.
35 36	401	
37 38	402	Safety reporting
39 40	403	AEs, SAEs and SUSARs:
41 42	404	Adverse events (AEs)
43 44	405	Adverse events are defined as any undesirable experience occurring to a subject during the
45 46	406	study, whether or not considered related to the investigational product. Since patients
47 48 40	407	admitted to an ICU are critically ill and present with many AEs, only possible adverse drug
49 50 51	408	related events (on days of study drug administration: prolonged QTc by EKG, muscle rigidity
52 53	409	and associated movements disorders [Simpson Angus Scale]) as indicated by the subject or
54 55	410	observed by the investigator or his staff occurring from the date of randomisation until 14
56 57	411	days later or discharge from ICU or death (whichever comes first), will be recorded in the
58 59	412	CRF. In addition, the following AEs will be assessed daily during 14 days after
60	413	randomisation: epilepsy, tachycardia, hypotension (not explained otherwise), hepatic
		15

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2 3	414	dysfunction (not explained otherwise), leucopenia (not explained otherwise), bronchospasms
4 5 6	415	(not explained otherwise).
7 8	416	
9 10	417	Serious adverse events (SAEs)
11 12	418	A SAE is any untoward medical occurrence or effect, occurring during the 14-day study
13 14	419	period at the ICU, that (the SAEs for the purpose of the study are shown in Italics per item)
15 16	420	results in death;
17 18 10	421	 death will always be reported as an SAE
20 21	422	 is life threatening (at the time of the event);
22 23	423	 ventricular arrhythmia or malignant neuroleptic syndrome
24 25 26 27 28 29	424	 requires hospitalisation or prolongation of existing inpatients' hospitalisation;
	425	• Not to be expected; only applicable when the site investigator is able to
	426	explicitly show a relationship
30 31	427	 results in persistent or significant disability or incapacity;
32 33	428	• Not to be expected; only applicable when the site investigator is able to
34 35 36	429	explicitly show a relationship
37 38 39 40 41 42 43 44 45 46	430	• is a congenital anomaly or birth defect; (Not applicable) or
	431	any other important medical event that did not result in any of the outcomes listed
	432	above due to medical or surgical intervention but could have been based upon
	433	appropriate judgement by the investigator.
	434	
47 48	435	Statistical analysis
49 50 51	436	Primary and secondary study parameter(s):
52 53	437	Statistical analysis will be done according to intention-to-treat-principle. All randomised
54 55	438	participants will be included. The primary outcome is DCFDs, defined as the number of days
56 57	439	in the first 14 days after randomisation during which the patient is alive without delirium and
58 59	440	not in coma from any cause (7). Patients who are discharged before the 14 day study period
60	441	has ended, will be recorded as delirium and coma-free after discharge (8, 35). Additionally,
		16

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2		
- 3 4	442	we will assume all patients who died within 14 days after randomisation to have 0 delirium
5 6	443	and coma free days (7). Differences between DCFDs between the haloperidol group and
7 8	444	placebo group will be analyzed using Poisson regression analysis, with adjustment for
9 10	445	differences in baseline characteristics between treatment groups (when present) and for the
11 12	446	different centers. We will collect data with regards to baseline demographics: age, sex,
13 14	447	admission diagnosis category, APACHE II and APACHE IV, SOFA, ICU days before study
15 16	448	entry and pre-admission delirium duration in participants with delirium on admission. Pre-
17 18	449	defined sub-analyses will include efficacy stratified by 1) agitated, mixed-type or hypoactive
19 20	450	delirium; 2) the presence of hallucinations or delusions; 3) delirium severity (based on ICDSC
21 22 22	451	score); and 4) sedation-related, hypoxic, metabolic or septic delirium. For cognitive and
23 24 25	452	functional outcomes assessed with designated test-batteries, non-parametric or parametric
26 27	453	tests will be used depending on normality of scaled test-results. Mortality risk will be
28 29	454	assessed as a binary end-point. A more detailed statistical analysis plan, to be drawn up
30 31	455	before Data Base Lock, will be drafted for publication separately.
32 33	456	
34 35	457	Interim analysis:
36 37	458	Pre-planned interim analyses will be performed at 1/3 and 2/3 of the trial's course (first
38 39	459	analysis ideally estimated at 6 months after start of trial), as determined by the DSMB charter
40 41	460	or otherwise when the DSMB requests it.
42 43	461	
45 46	462	Sample size calculation
47 48	463	To achieve statistically significant results with (p<.05) with a power of 90% and a true
49 50	464	treatment difference of one day for the primary outcome (from 3.2 DCFDs in the placebo
51 52	465	group to 4.2 in the haloperidol group, SD in both groups is equal to 4.2), 371 patients are
53 54	466	needed in each group (n=742). These estimates are derived from the previous
55 56	467	implementation study, which included 4727 patients in three 4-month periods in the same six
57 58	468	participating ICUs and found delirium incidence of 27% (and increase of DCFDs from 60% to
59 60	469	70%)(33). Consequently, presuming an informed consent rate of 40%, we need 18-months to
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encounter 1900 patients with a newly diagnosed delirium to include the required 742
patients. Because of estimated work-load due to follow-up visits, including e.g.
neurocognitive testing, we propose to select a convenience sample of 2/3 of ICU survivors
(estimated around 400 of 575 survivors) as a random sample for the cognitive, functional and
secondary outcome variables.
<u>ې</u>
Patient and Public Involvement
During the design and conduct of the study we involved two ex-ICU patients as patient-
perspective representatives. The primary research question, its outcome measures, and the
burden of the intervention have been assessed and found relevant by these patient-
representatives. The role and tasks of the patient-representatives for the study have been
detailed as: 1) to help select meaningful assessment-tools of patient and family experiences
during and after ICU stay, 2) act as liaison between the study management team and the
Dutch foundation "Family and patient Centered Intensive Care" (FCIC; one representative is
a formal representative for FCIC), 3) act as members of the Stakeholders group to provide
advice on the study contents, execution and course at on a regular basis to ensure the
patient and family perspective, 4) advise on the contents of the Patient Information Form
(PIF) and the informed consent procedure, 5) advise on ways to minimise loss to follow-up
for the functional and cognitive outcome assessments, 6) advise on contents and
organisation of symposia during the study on delirium and its consequences with the aim to
better inform participants of the study and their family members and maximize their
involvement, 7) advise on the contents of the supporting website of the trial. Study
participants will be informed about the most important results of the trial, either by post or
symposium, when they indicate this on the informed consent letter.
S.
ETHICS AND DISSEMINATION
The study has been approved by the Medical Ethics Committee of the Erasmus University

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495	ETHICS AND DISSEMINATION
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497	Medical Centre Rotterdam (MEC2017-511) and the Institutional Review Boards of

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participating sites. The study will be conducted according to the principles of the Declaration of Helsinki (version, date, see for the most recent version: www.wma.net) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts.

Recruitment and consent

Recruitment of eligible patients will be done upon admission. Informed consent for possible participation (i.e. only when participants develop delirium at the ICU) will be obtained from subjects who are not expected to leave the ICU within the first 24 hours after admission and are not yet delirious. The informed consent will be obtained from the patient or (if the patient is unable to consent) from patient's representative. This procedure of prior request for informed consent will facilitate randomisation when the patient indeed develops delirium, because randomisation can then be performed 24/7 since informed consent is already obtained and delirium often surfaces during the evening and night when obtaining informed consent is difficult. The informed consent procedure will be clearly delineated from the randomisation procedure. Importantly, when a patient with prior informed consent develops delirium and can thus be randomised, still a pre-randomisation check with regard to in- and exclusion criteria will be performed to confirm that the patient fulfils the inclusion, and not the exclusion criteria (because this may change over time). A team of dedicated research and ICU nurses and physicians (local PI, PhD student, PI, post-doc) will be trained to perform the informed consent procedures and help with the randomisations. Moreover, a 24/7 study consultation telephone number will be opened to help with problems or question during the study. A second type of randomisation concerns patients who are delirious upon admission to ICU. These patients' next-of-kin will be asked to grant permission to participate by means of informed consent when they are legally representative for the patients and the patient has no contraindications. After informed consent is obtained, the patient can be randomised.

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48	616	
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51	618	AUTHORS' CONTRIBUTIONS
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53	619	MJ developed the study protocol, edited and approved the final version, and was responsible
54 57		
22 56	620	tor tunding and supervising the study coordination. ZT contributed to the protocol
50 57		
58	621	development and study implementation. LS is responsible for study coordination. WR
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60	022	assisted with statistical analysis and NH assisted with pharmacological coordination. RU, AS,

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2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35	623	HP and JD were involved in the study design and protocol development. All authors
	624	contributed to the development and refinement of this study protocol. They have read and
	625	approved the final version of the protocol.
	626	
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	635	All involved local principal investigators (MB, AB, BM, JL, EK, FS, KS) and research nurses
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	637	be involved in executing the protocol at their sites and will be responsible for patient
	638	recruitment and data collection in their hospitals, along with follow up of study patients.
36 37	639	
38 39	640	Other members involved: C. Exler (11), E. van den Berg (12), J. van Meeteren (13), M.
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26 27	662	Netherlands.	
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	668	nterpretation of the data, or decision to submit results.	
40 41 42	669		
42 43 44 45 46	670	COMPETING INTERESTS STATEMENT	
	671	The authors declare that they have no competing interests.	
47 48	672		
49 50	673	LIST OF ABBREVIATIONS	
51 52		ABR ABR form, General Assessment and Registration form, is the application	
53 54		form that is required for submission to the accredited Ethics Committee	
55		(In Dutch, ABR = Algemene Beoordeling en Registratie)	
50 57		AE Adverse Event	
58 59		AR Adverse Reaction	
60		CA Competent Authority	
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3		CAM-ICU	Confusion Assessment Method for the ICU
4 5		ССМО	Central Committee on Research Involving Human Subjects; in Dutch:
6			Centrale Commissie Mensgebonden Onderzoek
8		CV	Curriculum Vitae
9 10		DSMB	Data Safety Monitoring Board
11		EU	European Union
12 13		EudraCT	European drug regulatory affairs Clinical Trials
14		EKG	Electrocardiography
15 16 17		GCP	Good Clinical Practice
18		IB	Investigator's Brochure
19 20		IC	Informed Consent
21		ICDSC	Intensive Care Delirium Screening Checklist
22 23		ICU	Intensive Care Unit
24		IMP	Investigational Medicinal Product
25 26		IMPD	Investigational Medicinal Product Dossier
27		METC	Medical research ethics committee (MREC); in Dutch: medisch ethische
28 29			toetsing commissie (METC)
30		PAD	Pain, agitation and delirium
32		RCT	Randomized Controlled Trial
33 34		(S)AE	(Serious) Adverse Event
35		S.O.P.	Standard Operating Procedure
36 37		SPC	Summary of Product Characteristics (in Dutch: officiële productinfomatie
38			IB1-tekst)
39 40		Sponsor	The sponsor is the party that commissions the organisation or
41		•	performance of the research, for example a pharmaceutical
42 43			company, academic hospital, scientific organisation or investigator. A
44 45			party that provides funding for a study but does not commission it is not
45 46			regarded as the sponsor, but referred to as a subsidising party.
47 48		SUSAR	Suspected Unexpected Serious Adverse Reaction
49			Torsade de Pointes
50 51		Whn	Porsonal Data Protoction Act (in Dutch: Wat Boscharming
52		wop	
53 54			Medical Research Involving Human Subjects Act (in Dutch: Wet Medicah
55		VIVIO	Medical Research involving Human Subjects Act (in Dutch: wet Medisch-
56 57	o= /		wetenschappelijk Underzoek met Mensen)
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59 60			

675 Table 1. Overview of timing of assessments, including required time investment per

676 visit/questionnaire.

Moment	Neurocognitive	Patient and	Functional	Cost effectivity	Other
(months)	tests	family	outcomes	questionnaires	
		experiences	(SF-36)	(EQ-5D-5L, iMTA	
		(time in min.)		MCQ, iMTA	
				PCQ)	
Enrolment					Informed
					consent,
					IQCODE-N,
		5			pregnancy
		0			test (if
		Ň.			applicable),
					EKG.
ICU study			0		CAM-ICU /
period (3x /			2.		ICDSC,
day)			0		RASS
ICU study			4		IMS, RCSQ.
period					Only when on
(once				0,	study
daily)				2/	medication:
				1	EKG,
					Simpson
					Angus Scale.
0		Patient: ICU-			
(discharge		MT (15) +			
from		DEQ (15)			
hospital)		Family: DEQ			
		(2)			
1				30 min.	

	3	45-60 min.	Patient: IES-R	10 min.	30 min.	
			(5) + ICU-MT			
			(15) + DEQ			
			(15)			
D 1			Family: IES-R			
2			(5) + CSI (5) +			
4			DEQ (2)			
5	6				30 min.	
3	12	45-60 min		10 min	30 min	
)		+3-00 mm.				
677	IQCODE-N	= Informant Questionna	ire on Cognitive Decl	line in the Eld	lerly – Dutch version	
<u> </u>	EKG = Elec	trocardiography				
⁺ 679	Neurocogr	nitive tests: Montreal Co	gnitive Assessment (I	MOCA), Rey A	Auditory Verbal Learning	Test, Semantic
, , 680	fluency, Di	git Span (WAIS-IV), Trailı	making tests A and B	, Boston nam	ing Test (short version), H	Hospital Anxiety
681	and Depre	ssion Scale (HADS)				
682	IMS = ICU	Mobility Scale, measures	s mobility during ICU	admission		
683	RCSQ = Ric	hards-Campbell Sleep Q	uestionnaire, measu	res quality of	sleep	
684	Simpson A	ngus Scale = measures n	nuscle rigidity and ot	her associate	d movements disorders	
685	ICU-MT= I	CU-Memory Tool, assess	es the experience an	d memories o	of ICU admission	
686	DEQ= Delir	rium Experience Questio	nnaire, measures exp	periences link	ed to delirium	
687	IES-R = Imp	pact of Event Scale Revis	ed, assesses distress	linked to a tr	aumatic experience (i.e.	experiencing
688	delirium)					
+ 5 689	CSI = Care	giver Strain Index, assess	es the strain experie	nced by the c	aregiver	
690	SF-36 = Sh	ort Form-36, measures t	he health-related qu	ality of life		
691	EQ-5D-5L =	= assesses the general he	ealth status			
692	iMTA MCC) = instituut Beleid & Ma	nagement Gezondhe	idszorg Medi	cal Consumption Questic	onnaire (health
693	care use)					
694	imta PCQ	= instituut Beleid & Mar	agement Gezondhei	dszorg Produ	ctivity Cost Questionnair	e (productivity
695	costs)					
696 697	With the e administer	xception of the neuroco ed at home. Real life vis	gnitive tests, all abov its only need to be pa	ve mentioned aid in order to	tools are questionnaires o perform the neurocogn	s that can be itive tests.

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Appendix 1: Participating hospitals

Erasmus MC Rotterdam

Albert Schweizer Hospital Dordrecht

Maasstad Hospital Rotterdam

IJsselland Hospital Capelle aan den IJssel

Ikazia Hospital Rotterdam

Franciscus Gasthuis Rotterdam

As of July 2019 two additional ICUs have started recruitment:

Jeroen Bosch Hospital, 's-Hertogenbosch

Radboud University Medical Center, Nijmegen

Appendix 2: Economic evaluation

ECONOMIC EVALUATION

General considerations

The primary economic analysis will be a trial-based **cost-utility analysis** from a societal and a healthcare perspective. This analysis will be performed according to the Dutch guidelines (1, 2). The time horizon will be 12 months after randomisation, in order to take all relevant costs and effects regarding the treatment procedure into account. Additionally, a **cost-effectiveness analysis** performed from a societal and health care perspective will be conducted, using delirium-free and coma-free days as outcomes.

If a difference in quality of life is observed at the end of the follow-up period, we will also perform a **model-based extrapolation** of costs and health benefits up to 5 years, exploring the following scenarios: (1) health benefit remain constant after the follow-up period, (2) health benefits are gradually phased out over the course of the modelling time, (3) health benefits are gradually phased out over the modelling time over the first year after follow-up, (4) health benefits abruptly disappear after the follow-up period, but costs remain until the end of the modelling period.

If treatment with haloperidol leads to better health outcomes at higher costs, or if it leads to worse health outcomes and cost savings, incremental cost-utility and incremental cost-effectiveness ratios will be calculated. These express the additional costs per unit of health gain (QALYs, deliriumfree days, coma-free days) or the savings per unit of health forgone. The uncertainty around the estimates will be addressed using bootstrapping for the analysis of costs and effects in the first 12 months, and using probabilistic sensitivity analysis in the extrapolation model.

Cost analysis

Healthcare costs will be calculated based on patient-level data on health-care utilization, which will be collected from hospital databases and questionnaires, to be filled out at regular intervals by patients and/or informal caregivers. Cost categories include medication, screenings, inpatient days, contacts with healthcare providers (GP, outpatient visits, and therapists). The questionnaire will also contain questions about absence from paid work by the patient and informal caregivers.

Costs will be calculated by multiplying resource utilization with the cost per unit of resource. Some unit costs will be taken from the 2016 Dutch Manual for Costing Studies(3), but the costs of inpatient days will be assessed following the micro-costing method, which is based on comprehensive 'bottom-up' analyses of the activities of staff and other resources that are used

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during those days. Medication prices will be based on the official list prices, including value added tax and increased by a standard prescription reimbursement for the pharmacist. The cost of production loss will be calculated according to the Friction Cost Approach.

Patient outcome analysis

The primary outcome measure in the economic evaluation is the difference in QALYs. The secondary effects are the delirium-free and coma-free days after treatment with haloperidol or placebo. As measuring QALYs in adult critically ill patients is not feasible at baseline, it is not possible to estimate the average number of QALYs for each treatment group. However, assuming that there is no difference at randomisation, it is possible to analyse the difference in quality of life at subsequent measurements in a multilevel regression model. This will enable us to calculate a difference in QALYs between the treatment groups over the total follow-up period, using linear intrapolation. HRQoL will be measured on t=1, 3, 6 and 12 months after randomization using the EQ-5D-5L instrument.

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2 3	Appendix 3: Haloperidal SPC
4	Appendix 5. halopendol see
5 6	See this weblink: <u>https://db.cbg-meb.nl/IB-teksten/h03185.pdf</u>
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Appendix 4: (Semi-) structured review of literature on efficacy and adverse events of haloperidol for delirium in adult critically ill patients

1. Haloperidol as a treatment for ICU delirium

Systematic review of randomised placebo-controlled trials assessing haloperidol for treatment of ICU delirium

Method: A biomedical Information Specialist (BIS) of the Erasmus Medical Center library performed a systematic search aimed at controlled studies on haloperidol for ICU delirium combining the subjects: delirium, ICU and haloperidol, or equivalent terms (see: Appendix for details). No distinction was made in the search between treatment or prevention trials.

Review: Since focus of the EuRIDICE study is on a haloperidol versus placebo comparison, the study selection for this summary is also focused on placebo-controlled haloperidol trials for the treatment of ICU delirium. Systematic reviews from the systematic search are used as a crosscheck to confirm completeness or provide additional insights. The search (total of yielded only 1 study. The MIND trial (2010) was a randomised placebo controlled feasibility, efficacy and safety trial of antipsychotics for ICU delirium in adult mechanically ventilated medical and surgical patients (1). It included three treatment arms (haloperidol, n=35; ziprasidone, n=30 and placebo, n=36) and used a well thought out design (excluding demented patients with a validated tool for cognitive dysfunction, using CAM-ICU as a validated screening tool, a clear protocol with regard to QTc prolongation and study drug dosing, measuring extrapyramidal symptoms with a validated scale and with number of days alive without delirium and coma as the primary outcome (indicating total burden of brain dysfunction, since only assessing delirium days may result in increased coma days and less delirium days being regarded as a – false – improvement). The study used oral haloperidol, no clear sedation protocol aimed at light sedation and crossover antipsychotics were allowed but discouraged. No clear differences were found in the three groups with regard to the primary outcome. Mean haloperidol dose was 15 mg a day but QTc prolongation and extrapyramidal symptoms did not differ between treatment groups. Other medications in this small trial did not differ between groups (propofol, opiates, benzodiazepines). It was concluded that a larger trial would be safe and feasible.

Overview of most recent guidelines' statements on haloperidol as treatment for ICU delirium Method: Pubmed search on published guidelines including ICU delirium and containing information on

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haloperidol. Search terms: guideline, delirium, ICU.

Review: Three recent guidelines were retrieved (2-4). In a Danish guideline (2015) no evidence is stated for pharmacological management(2). A German guideline (2015) advocates symptom-based therapy when delirium screening is positive with haloperidol as a first choice in case of delirium associated with psychotic symptoms only. The "Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit" (2013)(3) advocate avoiding 'antipsychotics' when risk of torsades de pointes or is present or either baseline QT prolongation or concomitant QT prolonging medication is used. It states that there is no evidence that haloperidol decrease delirium duration, which was perceived as the most relevant issue to address with regard to haloperidol treatment of ICU delirium.

Cochrane review(s)

Method: Search on Cochrane (http://www.cochranelibrary.com) for reviews with search term: 'delirium', does not elicit any results pertaining to pharmacological treatment of delirium nor haloperidol.

Review: no Cochrane reviews exist on (ICU) delirium and it's pharmacological management.

On-going trials

Method: A search for 'haloperidol' and 'delirium' in the following online trial databases (and including ICU patients); www.trialregister.nl (0 trials); www.clinicaltrials.gov (4 trials).

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Review: Four trials were retrieved from www.clinicaltrials.gov. One trial ('Haloquet') was not a truly placebo controlled trial because haloperidol was allowed ('as needed') in the placebo group and was last updated in 2013 but not published. It consisted of three treatments arms (also quetiapine) and aimed to include a total of 45 patients (and should thus be considered a pilot trial and not an efficacy trial). A second trial enrolled 40 patients and was completed in 2011 but not published. A third trial was a phase-2 safety/efficacy study enrolling 20 patients, last updated in 2007 and not published. The fourth trial ('The modifying the impact of ICU-associated neurological dysfunction-USA [MIND-USA] study') is currently recruiting (last verified May 2016 on September 14th). It is a multi-center double blind placebo-controlled trial aiming to enrol 561 patients in three treatment arms: haloperidol, ziprasidone and placebo, by the same research group that did the MIND trial. It includes cognitive and

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psychological follow-up at 12 months and is estimated to be completed July 2019. Maximum dose of haloperidol amounts to 10 mg IV q12 hours. Trial design is similar to the EuRIDICE trial, except for the patient experiences and perspective, and the fact that only patients on mechanical ventilation or in shock are included (i.e. the sickest ICU patients). The study protocol has not been published in a peerreviewed journal.

2. Haloperidol to prevent ICU delirium

Systematic review of randomised placebo-controlled trials assessing haloperidol for prevention of ICU delirium; including information from guidelines and Cochrane reviews

Method: A biomedical Information Specialist (BIS) of the Erasmus Medical Center library performed a systematic search aimed at controlled studies on haloperidol for ICU delirium combining the subjects: delirium, ICU and haloperidol, or equivalent terms (see: Appendix for details).

Review: the focus of this section is on randomised placebo-controlled prevention trials of haloperidol for ICU delirium. Three trials were retrieved. One trial included post-operative generally non-critically ill patients (5) and was not further considered for this review. The Hope-ICU trial (2013)(6) was a prophylactic study of haloperidol (2.5mg IV q8h, n=71) versus placebo (n=70) in adult mechanically ventilated ICU patients. The primary end-point of delirium (assessed with CAM-ICU) and coma free days did not differ between groups (5 days in both), but there was a 21% crossover rate with haloperidol in the placebo group. Secondary clinical endpoints such as length of stay at ICU or mortality did not differ but the trial was not powered on these outcomes. Another trial (2016)(7) including mechanically ventilated patients (n=68) with 'subsyndromal' delirium (=an Intensive Care Delirium Screening Checklist [ICDSC] score of 1-3 on a scale of 8, where 4 or more is compatible with delirium) used haloperidol 1mg IV q6h but did not find lower rate of progression to full delirium.

3. Haloperidol: adverse events versus treatment effects in the few available trials

The adverse events associated with haloperidol in the three aforementioned (small) trials (one treatment and two prevention trials) did not include QTc prolongation (with a threshold of >500 ms). In the Hope-ICU trial more opiates and sedatives were administered in the placebo-group but alfa-2

 agonists were not clearly protocolled, more agitation was present and 26% versus 11% antipsychotics' use in the placebo group. The subsyndromal delirium trial similarly found more agitation in the placebo group.

4. Healthcare perspective

A cost-effectiveness analysis of the Hope-ICU trial found that delirium increased cognitive dysfunction

at 6 months and reduced quality of life, suggestive of potential cost-effectiveness of haloperidol (8).

Acknowledgements:

Gerdien B. de Jonge (MSc), biomedical information specialist, Medical Library, Erasmus MC, is kindly acknowledged for her help in assembling the databases for the systematic review.

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Appendix 5: Drug Accountability

Upon randomisation, the study drug with the corresponding randomisation kit number 1-8 (based on 8 medication batches consisting of either haloperidol or placebo) will be obtained from the hospital pharmacy of each participating ICU. Each box from a batch/kit contains 10 ampules (5mg/1ml) of haloperidol or placebo. If all ampules are used, a new box from the same medication kit number with 10 ampules will be used. Study drugs are administered on prescription in the electronic patient data management system (PDMS) and are double-checked by ICU nurses before administration, which is similar to regular practice. Furthermore, the kit number was noted upon randomisation in the medical file and the kit number could be retrieved at any time from the PDMS after first prescription upon randomisation.

The research nurse of each participating ICU will record the number of the box with study drug for each patient in the CRF.

The research nurse of each participating ICU is responsible for retrieving the boxes with study drug. The amount of vials in the boxes will be counted for each patient and will be noted in the CRF.

The research nurse will return unused drug to the hospital pharmacy. The hospital pharmacy will destroy the vials with study drug and will also record this (double administration).

The pharmacist or another appropriate individual who is designated should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, problems and irregularities during injection, the maintenance of the blinding, and the return to the pharmacy of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial patients (if applicable). Investigators should maintain records that document adequately that the patients were provided the doses specified by the protocol and reconcile all investigational product(s).

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Appendix 6: Unblinding Procedure

2 The study treatment will be unblinded after Database Lock. While the safety of patients should 3 always take priority, maintenance of blinding is crucial to the integrity of a double-blind trial. Before 4 this planned unblinding, the blinding for a specific patient should only be broken when information 5 about the patient's protocol treatment is considered necessary to manage Serious Adverse Events 6 (emergency unblinding). Unblinding procedures should preferably be initiated only after consultation 7 of the principal investigator/coordinating investigator or his/her representative. To initiate an 8 emergency unblinding the pharmacy in charge of the randomisation list should be contacted. 9 Breaking the blinding on a patient will be logged and reported to the coordinating Investigator within 10 24 hours following the unblinding procedure, using the Emergency Unblinding Form. It is considered 11 a major protocol violation, after which the patient goes off protocol treatment (if applicable).

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

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		Reporting Item	Number
Administrative			
information			
Title	<u>#1</u>	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	<u>#2a</u>	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	<u>#2b</u>	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	<u>#3</u>	Date and version identifier	2
Funding	<u>#4</u>	Sources and types of financial, material, and other support	22
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1 2 3 4 5	Roles and responsibilities: contributorship	<u>#5a</u>	Names, affiliations, and roles of protocol contributors	1, 20
6 7 8 9 10 11 12	Roles and responsibilities: sponsor contact information	<u>#5b</u>	Name and contact information for the trial sponsor	1,2
13 14 15 16 17 18 19 20 21 22	Roles and responsibilities: sponsor and funder	<u>#5c</u>	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22
22 23 24 25 26 27 28 29 30	Roles and responsibilities: committees	<u>#5d</u>	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14
31 32	Introduction			
33 34 35 36 37 38 39	Background and rationale	<u>#6a</u>	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-5
40 41 42 43 44	Background and rationale: choice of comparators	<u>#6b</u>	Explanation for choice of comparators	3-5
45 46	Objectives	<u>#7</u>	Specific objectives or hypotheses	4
4/ 48 49 50 51 52 53 54	Trial design	<u>#8</u>	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
55	Methods:			
50 57 58	Participants,			
59 60	For p	beer revie	w only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

interventions, and outcomes			-
Study setting	<u>#9</u>	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	<u>#10</u>	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Protected by copy
Interventions: description	<u>#11a</u>	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10 ¹ ight, including
Interventions: modifications	<u>#11b</u>	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9-12 for uses related to
Interventions: adherance	<u>#11c</u>	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	t Superieur (AB text and data n
Interventions: concomitant care	<u>#11d</u>	Relevant concomitant care and interventions that are permitted or prohibited during the trial	nining, Al t
Outcomes	<u>#12</u>	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-9 7-9
Participant timeline	<u>#13</u>	Time schedule of enrolment, interventions (including any	9

- Pa run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
 - Sample size #14 Estimated number of participants needed to achieve study objectives and how it was determined, including For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Page 4	1 01 43		виј Орен	
1 2			clinical and statistical assumptions supporting any sample size calculations	
5 4 5 6 7	Recruitment	<u>#15</u>	Strategies for achieving adequate participant enrolment to reach target sample size	12
7 8 9 10 11 12 13	Methods: Assignment of interventions (for controlled trials)			
14 15 16 17 18 19 20 21 22 23 24 25	Allocation: sequence generation	<u>#16a</u>	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12-13
23 26 27 28 29 30 31	Allocation concealment mechanism	<u>#16b</u>	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12-13
32 33 34 35 36	Allocation: implementation	<u>#16c</u>	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12-13
37 38 39 40 41 42	Blinding (masking)	<u>#17a</u>	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12-13
43 44 45 46 47	Blinding (masking): emergency unblinding	<u>#17b</u>	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12-13
48 49 50 51 52 53 54	Methods: Data collection, management, and analysis			
55 56 57 58 59 60	Data collection plan	<u>#18a</u> beer revie	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate w only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	7-9

			BMJ Open	Page	e 42 of 43 መ
1 2 3 4 5 6 7			measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol		3MJ Open: first publishe
8 9 10 11 12 13	Data collection plan: retention	<u>#18b</u>	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13-14	d as 10.1136/bmjop Protected by
15 16 17 18 19 20 21 22	Data management	<u>#19</u>	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12, 15	oen-2019-036735 on 23 S r copyright, including fo
23 24 25 26 27 28 29	Statistics: outcomes	<u>#20a</u>	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16	September 2020. Do Enseignement Si or uses related to te:
30 31 32 33	Statistics: additional analyses	<u>#20b</u>	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16-17	wnloaded uperieur (<i>J</i> xt and dat
 33 34 35 36 37 38 39 40 41 	Statistics: analysis population and missing data	<u>#20c</u>	Definition of analysis population relating to protocol non- adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14	l from http://bmjopen.b ABES) . a mining, Al training, a
42 43 44 45 46 47 48 49 50 51 52 53 54	Data monitoring: formal committee	<u>#21a</u>	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14	nj.com/ on June 9, 2025 at Agence E ıd similar technologies.
54 55 56 57 58 59 60	Data monitoring: interim analysis	<u>#21b</u> peer revie	Description of any interim analyses and stopping guidelines, including who will have access to these w only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	16-17	3ibliographique de l

Page 4	3 of 43		BMJ Open	
1			interim results and make the final decision to terminate the trial	
3 4 5 6 7 8 9	Harms	<u>#22</u>	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15-16
10 11 12 13 14 15	Auditing	<u>#23</u>	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
16	Ethics and			
17 18 19	dissemination			
20 21 22	Research ethics approval	<u>#24</u>	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	17
23 24 25 26 27 28 29 30 31	Protocol amendments	<u>#25</u>	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	17
32 33 34 35 36	Consent or assent	<u>#26a</u>	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18
37 38 39 40 41	Consent or assent: ancillary studies	<u>#26b</u>	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
42 43 44 45 46 47 48	Confidentiality	<u>#27</u>	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18
49 50 51 52	Declaration of interests	<u>#28</u>	Financial and other competing interests for principal investigators for the overall trial and each study site	22
53 54 55 56 57 58	Data access	<u>#29</u>	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	-
59 50	For	peer revie	w only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

1 2 3 4 5	Ancillary and post trial care	<u>#30</u>	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
6 7 8 9 10 11 12 13	Dissemination policy: trial results	<u>#31a</u>	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	3
14 15 16 17	Dissemination policy: authorship	<u>#31b</u>	Authorship eligibility guidelines and any intended use of professional writers	-
18 19 20 21	Dissemination policy: reproducible research	<u>#31c</u>	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
22 23	Appendices			
24 25 26 27	Informed consent materials	<u>#32</u>	Model consent form and other related documentation given to participants and authorised surrogates	-
28 29 30 31 32 33	Biological specimens	<u>#33</u>	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA
34 35 36 37 38 39 40 41 42 43 445 46 47 48 50 51 52 53 54 55 56 57 58 59 60	None The SPIRIT check License CC-BY-ND 3.0. tool made by the EQUAT	list is di This ch <u>FOR Ne</u>	stributed under the terms of the Creative Commons Attribut ecklist can be completed online using <u>https://www.goodrep.</u> etwork in collaboration with <u>Penelope.ai</u>	ion <u>orts.org</u>

Efficacy of halopeRIdol to decrease the burden of Delirium In adult Critically ill patiEnts (EuRIDICE): study protocol for a prospective randomised multi-center double-blind placebo-controlled clinical trial in the Netherlands

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Primary Subject Heading :	Intensive care
Secondary Subject Heading:	Intensive care, Neurology, Mental health, Pharmacology and therapeutics
Keywords:	Delirium & cognitive disorders < PSYCHIATRY, INTENSIVE & CRITICAL CARE, Adult intensive & critical care < ANAESTHETICS, MENTAL HEALTH, Adult neurology < NEUROLOGY, THERAPEUTICS
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Efficacy of halopeRIdol to decrease the burden of Delirium In adult Critically ill patiEnts (EuRIDICE): study protocol for a prospective randomised multi-center double-blind placebo-controlled clinical trial in the Netherlands

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13 14	34	Protocol version: November 16th 20
15 16	35	
17 18	36	Word count: 4629 words
19 20	37	
21 22 22	38	ABSTRACT
23 24 25	39	Introduction: Delirium in critically ill a
25 26 27	40	increased mortality and greater cogni
28 29	41	recommendations advocate the use of
30 31	42	routine use of scheduled haloperidol
32 33	43	evidence regarding its ability to resolv
34 35	44	outcomes. This study aims to evaluat
36 37	45	of delirium in adult critically ill patients
38 39	46	Methods and analysis: EuRIDICE is
40 41	47	placebo-controlled, trial. Study popula
42 43	48	neurologic injury who have delirium b
44 45	49	Checklist (ICDSC) or Confusion Asse
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50 51 52	52	delirium resolution or ICU discharge.
53 54	53	(DCFD) up to 14 days after randomise
55 56	54	vear mortality; 2) cognitive and function
57 58	55	family delirium and ICU experience: 4
59 60	56	safety concerns associated with halor
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Protocol version: November 16th 2017, Version 2 Word count: 4629 words ABSTRACT **Introduction:** Delirium in critically ill adults is associated with prolonged hospital stay, ncreased mortality and greater cognitive and functional decline. Current practice guideline recommendations advocate the use of non-pharmacologic strategies to reduce delirium. The outine use of scheduled haloperidol to treat delirium is not recommended given a lack of evidence regarding its ability to resolve delirium nor improve relevant short and longer-term outcomes. This study aims to evaluate the efficacy and safety of haloperidol for the treatment of delirium in adult critically ill patients to reduce days spent with coma or delirium.

Methods and analysis: EuRIDICE is a prospective, multicentre, randomized, double-blind, placebo-controlled, trial. Study population consists of adult ICU patients without acute neurologic injury who have delirium based on a positive Intensive Care Delirium Screening Checklist (ICDSC) or Confusion Assessment Method for the ICU (CAM-ICU) assessment. ntervention is intravenous haloperidol 2.5 mg (or matching placebo) every 8 hours, titrated daily based on ICDSC or CAM-ICU positivity to a maximum of 5 mg every 8 hours, until delirium resolution or ICU discharge. Main study endpoint is delirium and coma free days (DCFD) up to 14 days after randomisation. Secondary endpoints include 1) 28-day and 1year mortality; 2) cognitive and functional performance at 3 and 12 months; 3) patient- and

- amily delirium and ICU experience; 4) psychological sequelae during and after ICU stay; 4)
- safety concerns associated with haloperidol use; and 5) cost-effectiveness. Differences in

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2 3 4	57	DCFDs between haloperidol and placebo group will be analysed using Poisson regression
- 5 6	58	analysis. Study recruitment started in February 2018 and continues.
7 8	59	Ethics and dissemination: The study has been approved by the Medical Ethics Committee
9 10	60	of the Erasmus University Medical Centre Rotterdam (MEC2017-511) and by the Institutional
11 12	61	Review Boards of the participating sites. Its results will be disseminated via peer-reviewed
13 14	62	publication and conference presentations.
15 16	63	Trial registration: ClinicalTrials, NCT03628391. Registered 14 August 2018 -
17 18	64	https://clinicaltrials.gov/ct2/show/NCT03628391. Netherlands Trial Registry, NTR6725.
19 20	65	Registered 29 September 2017 https://www.trialregister.nl/trial/6537.
21 22 22	66	
25 24 25	67	Strengths and limitations of this study
26 27	68	- This study is the first sufficiently powered randomised multi-center double-blind
28 29	69	placebo-controlled clinical trial in Europe;
30 31	70	- Extensive neurocognitive testing will be conducted with a valid test battery in
32 33	71	order to assess cognitive impairment at 3 and 12 months after ICU admission;
34 35	72	- We will assess patient- and family experiences associated with delirium as a
36 37	73	novel outcome;
38 39 40	74	- There are little data on the optimal haloperidol regimen in ICU patients; the
40 41 42	75	maximum haloperidol dose of 15mg/day in our study may still be subtherapeutic.
42 43 44	76	- Lack of true clinical equipoise among nurses and physicians regarding the use of
45 46	77	haloperidol may hamper motivation for the study.
47 48	78	
49 50	79	INTRODUCTION
51 52	80	Delirium occurs in up to 80% of patients admitted to the Intensive Care Unit (ICU) (1, 2) and
53 54	81	is associated with greater ICU and post-ICU mortality (2). Cognitive dysfunction and
55 56	82	functional decline after critical illness is common, frequently persists for months after ICU
57 58 59	83	discharge, and is worse among patients who experience delirium (2, 3). The symptoms and
60	84	sequelae of delirium, including fear, anxiety, disrupted sleep, and post-traumatic stress

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disorder, may persist for months after ICU discharge. The health and societal costs of
delirium are estimated to exceed \$10 billion per year in the USA alone (4).

Given the burden and costs of delirium in critically ill adults, substantial research efforts have been devoted to identify safe and effective strategies to treat it. Current evidence and practice guideline recommendations advocate the use of non-pharmacologic strategies to reduce delirium, including avoidance of benzodiazepine sedation, early mobilization and the use of sleep improvement protocols. The routine use of medication-based interventions to treat delirium, other than treatments to reduce the agitation that sometimes accompanies it, are not recommended (5, 6). The routine use of scheduled haloperidol to treat delirium is not currently recommended given a lack of current evidence regarding its ability to resolve delirium and its symptoms, nor improve relevant short and longer-term outcomes.

At the time this protocol was finalized, two randomized, placebo-controlled trials had evaluated haloperidol for ICU delirium prophylaxis or treatment and found haloperidol use did not affect days spent with delirium, days of mechanical ventilation, nor time spent in the ICU or hospital (7, 8). In one of these randomized controlled trials (RCTs), haloperidol use was associated with less agitation (7). Importantly, both studies were small (a combined total of 212 patients were enrolled), the ABCDEF bundle (a multimodal ICU bundle shown to reduce delirium by 50%)(9) was not routinely used, the effect of haloperidol on delirium-related symptoms was not evaluated, and the post-ICU, longer-term outcomes were not considered. Whether the response to haloperidol was different between patients with hyperactive versus hypoactive delirium was also not evaluated. The impact of haloperidol on patients'- and families' experiences with delirium after ICU discharge remains unknown. Whether long-term mortality is causally related to delirium or simply the persistent cognitive and functional decline associated with critical illness can only be established through a randomised trial (10). Moreover, the use of haloperidol in critically ill adults is not without potential safety concerns given it may prolong the QTc interval, induce extrapyramidal effects and cause oversedation. Despite haloperidol's lack of proven efficacy and the safety concerns

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2 3	112	associated with its use, haloperidol continues to be widely used in ICUs to treat of delirium
4 5	113	(11).
6 7	114	In light of the above evidence gaps that were identified at the time this trial was
8 9	115	conceptualized, there is a clear need for a large, multi-center, randomised controlled trial to
10 11	116	better define the efficacy and safety of haloperidol to treat delirium in critically ill adults. This
12 13	447	report describes the protocol for a large multicentre, readersized placebe controlled
14 15	117	report describes the protocol for a large, multicentre, randomized, placebo-controlled,
16 17	118	haloperidol delirium trial that recently started enrolling patients across multiple ICUs in the
18 19	119	Netherlands.
20 21	120	
22 23	121	METHODS AND ANALYSIS
24 25	122	Study design
26 27	123	Randomized, double-blind, placebo-controlled trial of haloperidol for the treatment of delirium
28 29	124	in patients admitted to one of six participating ICUs in the Rotterdam area in the Netherlands.
30 31	125	See Appendix 1 for the participating hospitals.
32 33	126	
34 35 26	127	Study population
36 37 28	128	Consecutive adults admitted to one of the participating ICUs.
38 39	129	
40 41 42	130	Eligibility criteria
43 44	131	Inclusion criteria for eligibility:
45 46	132	1. Age ≥ 18 years
47 48	133	2. Admitted to the ICU.
49 50	134	Exclusion criteria for eligibility:
51 52	135	1. Admitted to the ICU with an acute neurological diagnosis (including acute stroke,
53 54	136	traumatic brain injury, intracranial malignancy, anoxic coma). Prior non-acute stroke
55 56	137	or another neurological condition without cognitive deterioration is not an exclusion
57 58 59	138	criterion.
60	139	2. Pregnancy or lactation

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1 2			
2 3 4	140	3.	History of ventricular arrhythmia including "torsade de pointes" (TdP)
5 6	141	4.	Known allergy to haloperidol
7 8	142	5.	History of dementia or an Informant Questionnaire on Cognitive Decline in the Elderly
9 10	143		(IQCODE) score \geq 4 (12)
11 12	144	6.	History of malignant neuroleptic syndrome or parkinsonism (either Parkinson's
13 14	145		disease or another hypokinetic rigid syndrome)
15 16	146	7.	Schizophrenia or other psychotic disorder
17 18	147	8.	Inability to conduct valid delirium screening assessment (e.g. coma, deaf, blind) or
19 20 21	148		inability to speak the Dutch language
21 22 23	149	9.	Expected to die within 24 hours or leave the ICU within 24 hours
24 25	150		
26 27	151	<u>Inclusi</u>	on criteria for randomisation:
28 29 30 31	152	1.	Delirium, as assessed with the Intensive Care Delirium Screening Checklist (ICDSC ≥
	153		4) or the Confusion Assessment Method for the ICU (positive CAM-ICU assessment),
32 33	154		at the time of ICU admission or any ICU day after ICU admission.
34 35	155	2.	Written informed consent obtained from the patient or their legal representative
36 37 38	156	3.	All eligibility inclusion criteria (from above) are still met.
30 39 40	157	<u>Exclus</u>	sion criteria for randomisation:
40 41 42	158	1.	Prolonged QT-interval (QTc > 500ms)
43 44	159	2.	(recent) "Torsade de pointes" (TdP)
45 46	160	3.	(recent) Neuroleptic malignant syndrome or parkinsonism
47 48	161	4.	Evidence of acute alcohol (or substance) withdrawal requiring pharmacological
49 50	162		intervention (e.g. benzodiazepines or alpha-2 agonist) to treat
51 52	163	5.	The patient is expected to die within 24 hours or expected to leave the ICU within 24
53 54	164		hours.
55 56 57	165	6.	No (previously) signed informed consent by patient or representative
57 58 59	166	7.	Current participation in another intervention trial that is evaluating a medication,
60	167		device or behavioural intervention

1 2		
3	168	
5 6	169	Study outcomes
7 8 9 10	170	Main study outcome:
	171	ICU delirium- and coma free days (DCFDs) (up to 14 days after randomisation).
11 12	172	
13 14	173	Secondary study outcomes:
15 16 17 18 19 20 21	174	During ICU stay
	175	Richmond Agitation Sedation Scale (RASS)
	176	Maximum ICU Mobility Scale (IMS (13)) and day of max IMS.
21 22 23	177	Quality of sleep (Richards-Campbell Sleep Questionnaire [RCSQ] (14) and with a
24 25	178	visual analogue scale between 1-7 assessing the sleep quality according to the
26 27	179	nurse).
28 29	180	Use of "escape medication" for hallucinations and/or agitation (including atypical
30 31	181	antipsychotics, alpha-2 agonists, GABA-agonists, opiates and "open-label"
32 33 34 35 36 37 38	182	haloperidol).
	183	 Daily study drug dose corrected for body weight (mg/kg).
	184	Self-extubation rate, removal of invasive devices (intravenous/-arterial catheters,
39 40	185	drains and tubes).
41 42	186	Adverse drug associated events (prolonged QTc by EKG, muscle rigidity and other
43 44	187	associated movements disorders [Simpson Angus Scale (15)] and ventricular
45 46	188	arrhythmia's including torsade de pointes).
47 48 40	189	Blood pressure will be recorded previous to and 1 hour after the first study drug dose
49 50 51	190	(2.5mg equivalent) and 1 hour after the first 5mg equivalent.
52 53	191	Daily respiratory status (regarding endotracheal intubation and mechanical
54 55	192	ventilation)
56 57	193	Time from randomisation to first resolution of delirium
58 59 60	194	Time to "readiness for discharge from the ICU"

2 3 4	195	Hospital discharge
5 6 7 8 9 10	196	Patient and family-member well-being and experiences associated with delirium
	197	during and after ICU stay with the ICU Memory Tool (ICU-MT (16)) and Delirium
	198	Experience Questionnaire (DEQ (17)).
11 12	199	28 days after randomization
13 14	200	Mortality rate
15 16	201	3 months after randomization
17 18 10	202	Cognitive outcomes with a detailed cognitive assessment battery of validated and
19 20 21	203	repeatable measures of general cognition, memory, language, processing speed,
22 23	204	attention and executive functioning and mood (Montreal Cognitive Assessment
24 25	205	[MOCA](18), Rey Auditory Verbal Learning Test(19), Semantic fluency(20), Digit
26 27	206	Span [WAIS-IV](21), Trail making tests A and B(22), Boston naming Test [short
28 29	207	version](23), Hospital Anxiety and Depression Scale [HADS](24)).
30 31	208	• Functional outcomes and quality of life (Short Form-36 [SF-36](25)).
32 33	209	Patient and family-member well-being and experiences associated with delirium
34 35 36	210	during and after ICU stay with the ICU Memory Tool (ICU-MT (16)), Delirium
37 38	211	Experience Questionnaire (DEQ (17)) and Caregiver Strain Index (CSI (26)).
39 40	212	• Posttraumatic stress syndrome (PTSS) in participants and family-members with the
41 42	213	Impact of Event Scale – Revised (IES-R)(27).
43 44	214	12 months after randomization
45 46	215	Cognitive outcomes with a detailed cognitive assessment battery of validated and
47 48	216	repeatable measures of general cognition, memory, language, processing speed,
49 50 51	217	attention and executive functioning and mood (Montreal Cognitive Assessment
52 53	218	[MOCA](18), Rey Auditory Verbal Learning Test(19), Semantic fluency(20), Digit
54 55	219	Span [WAIS-IV](21), Trail making tests A and B(22), Boston naming Test [short
56 57	220	version](23), Hospital Anxiety and Depression Scale [HADS](24)).
58 59 60	221	• Functional outcomes and quality of life (Short Form-36 [SF-36](25)).

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Mortality rate

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223	
224	A cost-effectiveness analysis will be performed in collaboration with the Department of
225	Health Policy and Management of Erasmus University Rotterdam (see Appendix 2 for more
226	detailed explanation). The tools for the secondary outcomes are mentioned in Table 1 with
227	overview of timing of assessments.
228	
229	Treatment of subjects
230	Investigational product:
231	Name: Haldol (haloperidol)
232	Mechanism: butyrophenone-derived anti-psychotic with mainly dopamine-2 receptor
233	antagonistic properties
234	Placebo consists of sodium chloride for injection. Medical staff, patients and family will be
235	blinded to the product containing haloperidol/placebo.
236	
237	Summary of findings from clinical studies and of known and potential risks and benefits:
238	See: Summary of Product Characteristics (SPC) in Appendix 3 and Systematic Review
239	(Appendix 4).
240	
241	Dosages, dosage modifications and method of administration:
242	The following dosing scheme will be used: start with haloperidol/placebo (further called:
243	"study drug") 2.5mg IV q8h (because of delirium screening once every 8-hour shift) and
244	increase to a maximum dose of 5mg IV q8h when delirium persists during the next 8-hour
245	shift. Doses will be reduced (50% of dose) in the very old elderly (age \geq 80 years). The study
246	drug dose will be decreased (when dosage is 5mg IV q8h) or stopped (when dose is 2.5mg
247	IV q8h) when delirium has resolved (or is un-assessable due to coma) for the next 24 hours
248	(implying: three consecutive delirium assessments during three shifts). Dosages can be
249	lowered also at the discretion of the treating physician in case of evident rigidity, which is in

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line with current routine practice. Standard clinical practice for the administration of

4		
5 6	251	haloperidol will be followed.
7 8	252	
9 10	253	Description and justification of route of administration and dosage:
11 12	254	Administration of the study intervention via the IV (versus the oral or enteral) route is the
13 14	255	most feasible in critically ill patients – a population where gastrointestinal dysfunction is
15 16	256	prevalent and haloperidol absorption (i.e., bioavailability) could be compromised. The dose of
17 18	257	haloperidol or placebo equivalent to be used in the study is based on the following
19 20	258	consideration: 1. PK/PD; 2. Efficacy and 3. Safety. A (pilot) study in Erasmus Medical Center
21 22	259	(n=14 critically ill patients, abstract presented at European Society of Intensive Care
23 24 25	260	Medicine 2016) showed no adverse events (e.g. no QTc > 500ms), low serum levels (1.5-
25 26 27	261	2.2µg/L) and no clear relation between serum level and delirium resolution with haloperidol
28 29	262	dosages up to 2mg IV q8h (or: 3 x 2mg IV). A feasibility trial of haloperidol for ICU delirium
30 31	263	(MIND-trial (8)) that used an average total daily dosage of 15 mg orally found higher serum
32 33	264	levels (interquartile range 2.85-5.8 μ g/L). No differences were found in QTc prolongation
34 35	265	between treatment groups and placebo in this trial. None of these trials demonstrated
36 37	266	clinically important safety concerns associated with haloperidol administration. Finally, a
38 39	267	recently published trial of haloperidol for ICU delirium using haloperidol/placebo 10mg IV
40 41 42	268	q12h, did not report any safety issues, using a QTc cut-off for safety of 550ms, which may be
42 43 44	269	regarded an indirect signal that such dosages are feasible and safe (28). The maximum dose
45 46	270	of haloperidol of up to 5mg IV q8h was further chosen because a previous Dutch guideline
47 48	271	advocating the use of haloperidol recommended an IV haloperidol treatment dose of up to 20
49 50	272	mg/24h period (29). In our protocol, we chose q8h dosing (titrated up to 15mg daily) given
51 52	273	the greater potential susceptibility of critically ill adults to the side effects of haloperidol, and
53 54	274	the fact that this dosage is in line with existing haloperidol delirium protocols in several of the
55 56	275	participating ICUs.
57 58 59	276	

Patient assessments:

1

2		
- 3 4	278	Rigidity will be monitored with the Simpson-Angus scale (15) and the Barnes Akathisia
5 6 7 8	279	Rating Scale (30) (see "Secondary study endpoints") for study purposes only. The QTc
	280	interval will be measured daily before the administration of the second daily (afternoon) dose
9 10	281	using a 12-lead EKG. When the QTc interval is found to be prolonged (> 500ms or an
11 12	282	increase from baseline (=at randomisation) of \geq 60ms (31, 32)), all non-study medications
13 14	283	having the potential to prolong the QTc will be held if clinically feasible. A Standard Operating
15 16	284	Procedure (S.O.P.) lists the drugs known to prolong the QTc. Eight hours later, if QTc
17 18	285	prolongation persists, study medication will be held or tapered according to the S.O.P. and
19 20	286	only resumed when the EKGs (evaluation frequency increased to q8h in this situation) reveal
21 22 22	287	QTc prolongation to have dissipated.
25 24 25	288	
25 26 27	289	General medical management at participating ICUs:
28 29	290	In the six original participating ICUs, institutional delirium guidelines, based on the 2013 PAD
30 31	291	guidelines and a Dutch ICU delirium guideline, were rigorously implemented over a three-
32 33	292	year period (2012 to 2015) (6, 33, 34). During the inclusion period of the current trial, spot-
34 35	293	checks will be performed by members of the investigative team at each center to confirm
36 37	294	delirium screening accuracy, as a quality-of-assessments measure and these will be
38 39	295	documented in a qualitative manner.
40 41 42	296	
43 44	297	Preparation and labelling of Investigational Medicinal Product:
45 46	298	Preparation and labelling will be done by the trial pharmacist ("Apotheek A15") according to
47 48	299	GMP guidelines. Apotheek A15 is certified for these procedures. Trial medication will be
49 50	300	dispensed to the pharmacies of the trial sites by the Hospital Pharmacy of Erasmus MC. See
51 52	301	Appendix 5 for a description of the drug accountability.
53 54	302	
55 56	303	Escape medication:
57 58	304	Knowing that half the subjects will be administered placebo, we anticipate two issues may
59 60	305	affect the clinical management of enrolled patients: 1) agitation and 2) hallucinations.
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Agitation management will be based on the following principles: a) treat pain first with opioids; b) use alpha-2 agonist for agitation that either persists or is not caused by pain; c) GABA agonists (e.g. benzodiazepines or propofol) are discouraged, but can be used on a short-term basis for the treatment of severe agitation (RASS \geq 2) that cannot be effectively managed by other means. Hallucination management will be based on the following principles: a) pharmacological treatment may be withheld if the patient indicates they are not in distress; b) for a patient in distress, a low-dose atypical antipsychotic (e.g., quetiapine 12.5mg q8h) may be administered on a short-term basis until the distress resolves. Because of the pragmatic design of this trial, within these boundaries, the treatment and dose of escape medication is left to the treating physician, since these are part of routine practice. However, before start of randomisation these management principles for agitation and hallucination will be thoroughly implemented first with the help of detailed S.O.P.'s to enhance uniformity in participating centres. Adherence to escape medication regimens will be closely monitored. Open-label haloperidol administration is strongly discouraged during the trial but can be used if the ICU team considers it necessary for acute breakthrough delirium symptoms that cannot be managed within the management boundaries outlined above. Open-label haloperidol will be documented. Randomisation, blinding and treatment allocation Legal representatives of eligible patients (when the patient is sedated or otherwise temporarily unable to consent) or the patient him-/herself will be asked for informed consent shortly after admission when the patient has no delirium, or as soon as possible after admission when the patient already has delirium. Appendix 6 contains an example of the patient consent form. In this study the presence of delirium will be considered to be confirmed when the beside nurse deemed the patient to have delirium based on assessment with the ICDSC or CAM-ICU, given the previous large-scale implementation project (33).

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Delirious patients who fulfil all inclusion but no exclusion criteria, and for whom written informed consent has been obtained (as recorded in medical file), will be randomised. Randomisation coordination and start of a new Case Record Form (CRF) will be guided by the Electronic Data Capture (EDC) system of ALEA, constructed by the Clinical Trial Center (CTC) of the Erasmus Medical Center and calibrated with the coordinating (Erasmus MC) and local pharmacies. We will randomise the recruited patients using a block design of 8 patients in one block, and one block is assigned to a center. We will have 8 batches (numbered 1 through 8) of treatment and placebo, with 4 batches of placebo and 4 treatment (haloperidol). Each block will have a random assignment of 8 batch numbers, having four placebo and four haloperidol patients included (a combination of 1 to 4 and 5 to 8 in random order). After 8 patients are included in the study (i.e., a block is full), a new block will be assigned to a center.

Upon randomisation, the study drug with the corresponding randomisation kit number 1-8 (based on 8 medication batches consisting of either haloperidol or placebo) will be obtained from the hospital pharmacy of each participating ICU. Each box from a batch/kit contains 10 ampules (5mg/1ml) of haloperidol or placebo. If all ampules are used, a new box from the same medication kit number with 10 ampules will be used. Study drugs are administered on prescription in the electronic patient data management system (PDMS) and are double-checked by ICU nurses before administration, which is similar to regular practice. Furthermore, the kit number was noted upon randomisation in the medical file and the kit number could be retrieved at any time from the PDMS after first prescription upon randomisation.

Blinding of the medication will be performed by the pharmacy, based on a Blinding of the medication will be performed by the pharmacy, based on a randomisation list that will be generated electronically through a randomisation module in the EDC system of ALEA. Randomisation will be stratified per study center (i.e. equal number of patients in both study groups, see "statistical analysis" paragraph). Only the involved pharmacists and the trial statistician are aware of the contents of each medication kit. Only the local (site) pharmacists are able to unblind study treatment of a patient in case of an

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3 4 5 6 7 8 9 10 11 23 14 15 16 7 8 9 20 21 22 24 25 26 7 8 9 30 31 23 34 35 36 7 8 9 0 11 21 31 4 56 7 8 9 0 11 21 31 4 56 7 8 9 0 11 21 31 4 56 7 8 9 0 11 21 31 4 56 7 8 9 0 11 22 23 24 25 26 7 8 9 30 31 23 34 5 36 37 8 9 0 41 42 34 45 67 8 9 0 11 22 23 24 25 26 7 8 9 30 31 23 34 5 36 7 8 9 0 41 42 34 45 67 8 9 0 11 22 23 24 25 26 7 8 9 30 31 23 34 5 36 7 8 9 0 41 42 34 45 67 7 8 9 0 11 22 23 24 25 26 7 8 9 30 31 23 34 5 36 7 8 9 0 41 42 34 45 56 7 7 8 9 0 11 22 33 45 56 7 8 9 0 11 22 33 45 56 7 8 9 0 11 22 33 45 56 7 8 9 0 11 22 33 45 56 7 8 9 0 11 22 33 45 56 7 8 9 0 11 22 3 34 5 56 7 8 9 0 11 22 3 34 5 56 7 8 9 0 11 22 3 34 5 56 7 8 9 0 11 25 3 34 5 56 7 8 9 0 11 25 3 4 5 56 7 8 9 0 11 25 3 4 5 56 7 8 9 0 11 25 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	361	emergency. Except for the hospital's pharmacist responsible for the randomisation list, all
	362	other involved personnel with the study, caregivers, patients or their representatives will
	363	remain unaware of the treatment groups until the time of Database Lock. The Unblinding
	364	procedure is specified in Appendix 7.
	365	Follow-up procedures will be performed according to designated S.O.P.'s. When possible
	366	and preferred by patients or families, questionnaires will be sent or visits planned at home
	367	when possible, e.g. for incapacitated participants.
	368	
	369	Withdrawal of individual subjects
	370	Subjects can leave the study at any time for any reason if they wish to do so without any
	371	consequences. The investigator can decide to withdraw a subject from the study for urgent
	372	medical reasons.
	373	
	374	Follow-up of subjects withdrawn from treatment
	375	Data of withdrawn patients will remain in the database for statistical analysis purposes but
	376	will not be subject to follow-up. When patients specifically withdraw their consent for usage of
	377	their data, these data will be removed from the database and excluded from all analyses.
	378	
	379	Premature termination of the study
	380	The sponsor may decide to terminate the study prematurely based on the following criteria:
	381	• There is evidence of an unacceptable risk for study patients (i.e. safety issue)
	382	There is reason to conclude that continuation of the study cannot serve a scientific
	383	purpose following confirmation of the Data Safety Monitoring Board (DSMB)
	384	The DSMB recommends to end the trial based on viable arguments other than
	385	described above.
55 56 57	386	
57 58	387	The following stopping rules have been determined by the DSMB and have been laid down
60	388	in a DSMB charter:
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3 4	389	• Early stopping of one individual participant, for example, to clear benefit or harm of a			
5 6 7 8 9 10 11 12 13 14	390	treatment or the occurrence of serious adverse reactions or events in one patient. In			
	391	this case de-blinding of this single patient may be necessary.			
	392	• Stopping of the trial as a whole to clear benefit or harm of a treatment or the			
	393	occurrence of serious adverse reactions or events. As a result, further patient			
	394	enrolment will be stopped. Deblinding may be necessary for all patients.			
15 16	395				
17 18	396	Reasons to stop the study include:			
19 20	397	Advice to do so from DSMB			
21 22	398	 Interim analysis shows a significant benefit difference between the treatment groups 			
23 24	399	which will not be expected to change after inclusion of all subject as per the power			
25 26	400	analysis			
27 28	401				
29 30 21	402	SUSAR's are not expected due to the vast experience in clinical practice with the study drug			
 31 32 33 34 35 36 37 38 39 40 41 42 43 	40.3	(haloperidol)			
	404				
	405	If the study is terminated the Medical Ethics Committees of all participating bospital and the			
	400	CCMO will be notified			
	400				
	407				
44 45	408	Safety reporting			
46 47	409	AES, SAES and SUSARS:			
48 49	410	Adverse events (AEs)			
50 51	411	Adverse events are defined as any undesirable experience occurring to a subject during the			
52 53	412	study, whether or not considered related to the investigational product. Since patients			
54 55	413	admitted to an ICU are critically ill and present with many AEs, only possible adverse drug			
56 57	414	related events (on days of study drug administration: prolonged QTc by EKG, muscle rigidity			
58 59	415	and associated movements disorders [Simpson Angus Scale]) as indicated by the subject or			
60	416	observed by the investigator or his staff occurring from the date of randomisation until 14			
		15			

3 4	417	days later or discharge from ICU or death (whichever comes first), will be recorded in the				
5 6 7 8	418	CRF. In addition, the following AEs will be assessed daily during 14 days after				
	419	randomisation: epilepsy, tachycardia, hypotension (not explained otherwise), hepatic				
9 10	420	dysfunction (not explained otherwise), leucopenia (not explained otherwise), bronchospasms				
11 12	421	(not explained otherwise).				
13 14 15	422					
15 16 17	423	Serious adverse events (SAEs)				
17 18 19	424	A SAE is any untoward medical occurrence or effect, occurring during the 14-day study				
20 21	425	period at the ICU, that (the SAEs for the purpose of the study are shown in <i>Italics</i> per item)				
22 23	426	results in death;				
24 25	427	 death will always be reported as an SAE 				
26 27	428	 is life threatening (at the time of the event); 				
28 29	429	 ventricular arrhythmia or malignant neuroleptic syndrome 				
30 31 22	430	 requires hospitalisation or prolongation of existing inpatients' hospitalisation; 				
32 33 34	431	• Not to be expected; only applicable when the site investigator is able to				
35 36	432	explicitly show a relationship				
37 38	433	 results in persistent or significant disability or incapacity; 				
39 40	434	• Not to be expected; only applicable when the site investigator is able to				
41 42	435	explicitly show a relationship				
43 44	436	• is a congenital anomaly or birth defect; (<i>Not applicable</i>) or				
45 46	437	any other important medical event that did not result in any of the outcomes listed				
47 48 40	438	above due to medical or surgical intervention but could have been based upon				
49 50 51	439	appropriate judgement by the investigator.				
52 53	440					
53 54 55 56 57 58 59	441	Statistical analysis				
	442	Primary and secondary study parameter(s):				
	443	Statistical analysis will be done according to intention-to-treat-principle. All randomised				
60	444	participants will be included. The primary outcome is DCFDs, defined as the number of days				
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in the first 14 days after randomisation during which the patient is alive without delirium and not in coma from any cause (7). Patients who are discharged before the 14 day study period has ended, will be recorded as delirium and coma-free after discharge (8, 35). Additionally, we will assume all patients who died within 14 days after randomisation to have 0 delirium and coma free days (7). Differences between DCFDs between the haloperidol group and placebo group will be analyzed using Poisson regression analysis, with adjustment for differences in baseline characteristics between treatment groups (when present) and for the different centers. We will collect data with regards to baseline demographics: age, sex, admission diagnosis category, APACHE II and APACHE IV, SOFA, ICU days before study entry and pre-admission delirium duration in participants with delirium on admission. Pre-defined sub-analyses will include efficacy stratified by 1) agitated, mixed-type or hypoactive delirium; 2) the presence of hallucinations or delusions; 3) delirium severity (based on ICDSC score: low delirium severity = mean ICDSC score of 4 to 5; medium delirium severity = mean ICDSC score 5 to 7; or high delirium severity = ICDSC score 7 to 8); and 4) sedation-related, hypoxic, metabolic or septic delirium. For cognitive and functional outcomes assessed with designated test-batteries, non-parametric or parametric tests will be used depending on normality of scaled test-results. Mortality risk will be assessed as a binary end-point. A more detailed statistical analysis plan, to be drawn up before Data Base Lock, will be drafted for publication separately.

465 Interim analysis:

Pre-planned interim analyses will be performed at 1/3 and 2/3 of the trial's course (first
analysis ideally estimated at 6 months after start of trial), as determined by the DSMB charter
or otherwise when the DSMB requests it.

₅₄ 469

470 Sample size calculation

471 To achieve statistically significant results with (p<.05) with a power of 90% and a true
 472 treatment difference of one day for the primary outcome (from 3.2 DCFDs in the placebo)

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3 4 5 6 7 8 9 10 11 12 13 14 15 16	473	group to 4.2 in the haloperidol group, SD in both groups is equal to 4.2), 371 patients are
	474	needed in each group (n=742). These estimates are derived from the previous
	475	implementation study, which included 4727 patients in three 4-month periods in the same six
	476	participating ICUs and found delirium incidence of 27% (and increase of DCFDs from 60% to
	477	70%)(33). Consequently, presuming an informed consent rate of 40%, we need 18-months to
	478	encounter 1900 patients with a newly diagnosed delirium to include the required 742
	479	patients. Because of estimated work-load due to follow-up visits, including e.g.
17 18 10	480	neurocognitive testing, we propose to select a convenience sample of 2/3 of ICU survivors
19 20 21	481	(estimated around 400 of 575 survivors) as a random sample for the cognitive, functional and
21 22 23 24 25 26 27 28 29	482	secondary outcome variables.
	483	
	484	Patient and Public Involvement
	485	During the design and conduct of the study we involved two ex-ICU patients as patient-
30 31	486	perspective representatives. The primary research question, its outcome measures, and the
32 33	487	burden of the intervention have been assessed and found relevant by these patient-
34 35	488	representatives. The role and tasks of the patient-representatives for the study have been
36 37 28	489	detailed as: 1) to help select meaningful assessment-tools of patient and family experiences
30 39 40	490	during and after ICU stay, 2) act as liaison between the study management team and the
41 42	491	Dutch foundation "Family and patient Centered Intensive Care" (FCIC; one representative is
43 44	492	a formal representative for FCIC), 3) act as members of the Stakeholders group to provide
45 46	493	advice on the study contents, execution and course at on a regular basis to ensure the
47 48	494	patient and family perspective, 4) advise on the contents of the Patient Information Form
49 50	495	(PIF) and the informed consent procedure, 5) advise on ways to minimise loss to follow-up
51 52	496	for the functional and cognitive outcome assessments, 6) advise on contents and
53 54	497	organisation of symposia during the study on delirium and its consequences with the aim to
55 56	498	better inform participants of the study and their family members and maximize their
57 58 59 60	499	involvement, 7) advise on the contents of the supporting website of the trial. Study
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participants will be informed about the most important results of the trial, either by post or symposium, when they indicate this on the informed consent letter. ETHICS AND DISSEMINATION The study has been approved by the Medical Ethics Committee of the Erasmus University Medical Centre Rotterdam (MEC2017-511) and the Institutional Review Boards of participating sites. The study will be conducted according to the principles of the Declaration of Helsinki (version, date, see for the most recent version: www.wma.net) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts. **Recruitment and consent** Recruitment of eligible patients will be done upon admission. Informed consent for possible participation (i.e. only when participants develop delirium at the ICU) will be obtained from subjects who are not expected to leave the ICU within the first 24 hours after admission and are not yet delirious. The informed consent will be obtained from the patient or (if the patient is unable to consent) from patient's representative. This procedure of prior request for informed consent will facilitate randomisation when the patient indeed develops delirium, because randomisation can then be performed 24/7 since informed consent is already obtained and delirium often surfaces during the evening and night when obtaining informed consent is difficult. The informed consent procedure will be clearly delineated from the randomisation procedure. Importantly, when a patient with prior informed consent develops delirium and can thus be randomised, still a pre-randomisation check with regard to in- and exclusion criteria will be performed to confirm that the patient fulfils the inclusion, and not the exclusion criteria (because this may change over time). A team of dedicated research and ICU nurses and physicians (local PI, PhD student, PI, post-doc) will be trained to perform the informed consent procedures and help with the randomisations. Moreover, a 24/7 study consultation telephone number will be opened to help with problems or question during the

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2		
3	528	study. A second type of randomisation concerns patients who are delirious upon admission
4		
5 6	529	to ICU. These patients' next-of-kin will be asked to grant permission to participate by means
7	520	of informed concert when they are legally representative for the patients and the patient has
8	530	or informed consent when they are legally representative for the patients and the patient has
9	531	no contraindications. After informed consent is obtained, the patient can be randomised
10	001	
11	532	
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14	533	REFERENCES
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1 2 3	625	
4 5 6 7 8	626	AUTHORS' CONTRIBUTIONS
	627	MJ developed the study protocol, edited and approved the final version, and was responsible
9 10	628	for funding and supervising the study coordination. ZT contributed to the protocol
11 12	629	development and study implementation. LS is responsible for study coordination. WR
13 14 15 16	630	assisted with statistical analysis and NH assisted with pharmacological coordination. RO, AS,
	631	HP and JD were involved in the study design and protocol development. All authors (LS, ZT,
17 18 19	632	JD, RO, HP, AS, NH, WR, DG, MJ) contributed to the development and refinement of this
20 21	633	study protocol. They have read and approved the final version of the protocol.
22 23	634	
23 24 25	635	Acknowledgements
26 27	636	EuRIDICE study group authors:
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 30 31 32 33 34 35 36 37 38 39 40 41 42 	638	(9), B.J.M. van der Meer (8), H. Ponssen (4), F.J. Schoonderbeek (10), K.S. Simons (16).
	639	Local research nurses: E. Berger (7), A. Bouman (16), M. Campo (8), D. van Duijn (1), H.
	640	Embden – van Donk (10), D. van de Graaf (9), E. Hoogendoorn (4), P. Ormskerk (1), N.
	641	Roovers (15), E. Toscano (8), A. Vileito (1), T. van Zuylen (16).
	642	
	643	All involved local principal investigators (MB, AB, BM, JL, EK, FS, KS) and research nurses
43 44	644	(EB, AB, DD, HE, DG, PO, NR, AV, MC, ET, EH, TZ) have facilitated visits at their site, will
45 46	645	be involved in executing the protocol at their sites and will be responsible for patient
47 48	646	recruitment and data collection in their hospitals, along with follow up of study patients.
49 50	647	
51 52	648	Other members involved: C. Exler (11), E. van den Berg (12), J. van Meeteren (13), M.
53 54	649	Koopmanschap (14).
56 57	650	Patient representatives: I. Nutma and E. Kuijper.
58 59 60	651	

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32 33	666	HTA, Rotterdam, The Netherlands, Netherlands
34 35	667	15) Radboud University Medical Center, Department of Inte
30	, 668	The Netherlands
39	, 9 669	16) Jeroen Bosch Hospital, Department of Intensive Care M
41	, 670	Netherlands.
43	671	
45 46	672	FUNDING STATEMENT
47 48	673	A grant has been provided by ZonMw – The Netherlands O
49 50	674	and Organisation. ZonMw project number: 848041001. This
51 52	675	the design of this study and will not have any role during its
53 54	676	interpretation of the data, or decision to submit results.
55 56	677	
57	678	COMPETING INTERESTS STATEMENT
60	, 9 679	The authors declare that they have no competing interests.

1 2

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000						
681	LIST OF ABBREVIATIONS					
	ABR	ABR form, General Assessment and Registration form, is the application				
		form that is required for submission to the accredited Ethics Committee				
		(In Dutch, ABR = Algemene Beoordeling en Registratie)				
	AE	Adverse Event				
	AR	Adverse Reaction				
	CA	Competent Authority				
	CAM-ICU	Confusion Assessment Method for the ICU				
	ССМО	Central Committee on Research Involving Human Subjects; in Dutch:				
		Centrale Commissie Mensgebonden Onderzoek				
	CV	Curriculum Vitae				
	DSMB	Data Safety Monitoring Board				
	EU	European Union				
	EudraCT	European drug regulatory affairs Clinical Trials				
	EKG	Electrocardiography				
	GCP	Good Clinical Practice				
	IB	Investigator's Brochure				
	IC	Informed Consent				
	ICDSC	Intensive Care Delirium Screening Checklist				
	ICU	Intensive Care Unit				
	IMP	Investigational Medicinal Product				
	IMPD	Investigational Medicinal Product Dossier				
	METC	Medical research ethics committee (MREC); in Dutch: medisch ethische				
		toetsing commissie (METC)				
	PAD	Pain, agitation and delirium				
	RCT	Randomized Controlled Trial				
	(S)AE	(Serious) Adverse Event				
	S.O.P.	Standard Operating Procedure				
	SPC	Summary of Product Characteristics (in Dutch: officiële productinfomatie				
		IB1-tekst)				
	Sponsor	The sponsor is the party that commissions the organisation or				
		performance of the research, for example a pharmaceutical				

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		company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not
		regarded as the sponsor, but referred to as a subsidising party.
	SUSAR	Suspected Unexpected Serious Adverse Reaction
	TdP	Torsade de Pointes
	Wbp	Personal Data Protection Act (in Dutch: Wet Bescherming
		Persoonsgevens)
	WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-
		wetenschappelijk Onderzoek met Mensen)
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683 Table 1. Overview of timing of assessments, including required time investment per

684 visit/questionnaire.

Moment	Neurocognitive	Patient and	Functional	Cost effectivity	Other
(months)	tests	family	outcomes	questionnaires	
		experiences	(SF-36)	(EQ-5D-5L, iMTA	
		(time in min.)		MCQ, iMTA	
		C		PCQ)	
Enrolment					Informed
					consent,
			2		IQCODE-N,
				0	pregnancy
					test (if
					applicable),
					EKG.
ICU study					CAM-ICU /
period (3x /					ICDSC,
day)					RASS
ICU study					IMS, RCSQ.
period					Only when on
(once					study
daily)					medication:

						EKG,	
						Simpson	
						Angus Scale.	
	0		Patient: ICU-				
	(discharge		MT (15) +				
	from		DEQ (15)				
	hospital)		Family: DEQ				
			(2)				
	1				30 min.		
	3	45-60 min.	Patient: IES-R	10 min.	30 min.		
			(5) + ICU-MT				
			(15) + DEQ				
			(15)				
			Family: IES-R				
			(5) + CSI (5) +				
			DEQ (2)	2.			
	6			6	30 min.		
	12	45-60 min.		10 min.	30 min.		
685	IQCODE-N = Info	ormant Questionnaire	e on Cognitive Decl	line in the Elder	ly – Dutch version	11	
686	EKG = Electroca	rdiography					
687	Neurocognitive	tests: Montreal Cogn	itive Assessment (I	MOCA), Rey Aud	ditory Verbal Learning	Test, Semantic	
688	fluency, Digit Sp	oan (WAIS-IV), Trailma	aking tests A and B	, Boston naming	g Test (short version), H	Hospital Anxiety	
689	and Depression	Scale (HADS)					
690	IMS = ICU Mobil	lity Scale, measures n	nobility during ICU	admission			
691	RCSQ = Richards	s-Campbell Sleep Que	estionnaire, measu	res quality of sle	еер		
692	Simpson Angus	Scale = measures mu	scle rigidity and ot	her associated r	novements disorders		
693	ICU-MT= ICU-M	emory Tool, assesses	the experience an	d memories of	CU admission		
694	DEQ= Delirium E	Experience Questionr	naire, measures exp	periences linked	l to delirium		
695	IES-R = Impact of Event Scale Revised, assesses distress linked to a traumatic experience (i.e. experiencing						
696	delirium)						

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- 697 CSI = Caregiver Strain Index, assesses the strain experienced by the caregiver
- 5 698 SF-36 = Short Form-36, measures the health-related quality of life
- 7 699 EQ-5D-5L = assesses the general health status 8
- 9 700 iMTA MCQ = instituut Beleid & Management Gezondheidszorg Medical Consumption Questionnaire (health 10
- 11 701 care use)
- 13 702 iMTA PCQ = instituut Beleid & Management Gezondheidszorg Productivity Cost Questionnaire (productivity
- 15 703 costs)

With the exception of the neurocognitive tests, all above mentioned tools are questionnaires that can be administered at home. Real life visits only need to be paid in order to perform the neurocognitive tests.

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3 A	Appendix 1: Participating hospitals
5 6	Erasmus MC Rotterdam
7 8	Albert Schweizer Hospital Dordrecht
9 10 11	Maasstad Hospital Rotterdam
12 13	IJsselland Hospital Capelle aan den IJssel
14 15	Ikazia Hospital Rotterdam
10	Franciscus Gasthuis Rotterdam
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20	
21 22	As of July 2019 two additional ICUs have started recruitment:
23 24	Jeroen Bosch Hospital, 's-Hertogenbosch
25	Dadhaud University Madical Contar Nijmagan
26	Rauboud University Medical Center, Nijmegen
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Appendix 2: Economic evaluation

ECONOMIC EVALUATION

General considerations

The primary economic analysis will be a trial-based **cost-utility analysis** from a societal and a healthcare perspective. This analysis will be performed according to the Dutch guidelines (1, 2). The time horizon will be 12 months after randomisation, in order to take all relevant costs and effects regarding the treatment procedure into account. Additionally, a **cost-effectiveness analysis** performed from a societal and health care perspective will be conducted, using delirium-free and coma-free days as outcomes.

If a difference in quality of life is observed at the end of the follow-up period, we will also perform a **model-based extrapolation** of costs and health benefits up to 5 years, exploring the following scenarios: (1) health benefit remain constant after the follow-up period, (2) health benefits are gradually phased out over the course of the modelling time, (3) health benefits are gradually phased out over the modelling time over the first year after follow-up, (4) health benefits abruptly disappear after the follow-up period, but costs remain until the end of the modelling period.

If treatment with haloperidol leads to better health outcomes at higher costs, or if it leads to worse health outcomes and cost savings, incremental cost-utility and incremental cost-effectiveness ratios will be calculated. These express the additional costs per unit of health gain (QALYs, deliriumfree days, coma-free days) or the savings per unit of health forgone. The uncertainty around the estimates will be addressed using bootstrapping for the analysis of costs and effects in the first 12 months, and using probabilistic sensitivity analysis in the extrapolation model.

Cost analysis

Healthcare costs will be calculated based on patient-level data on health-care utilization, which will be collected from hospital databases and questionnaires, to be filled out at regular intervals by patients and/or informal caregivers. Cost categories include medication, screenings, inpatient days, contacts with healthcare providers (GP, outpatient visits, and therapists). The questionnaire will also contain questions about absence from paid work by the patient and informal caregivers.

Costs will be calculated by multiplying resource utilization with the cost per unit of resource. Some unit costs will be taken from the 2016 Dutch Manual for Costing Studies(3), but the costs of inpatient days will be assessed following the micro-costing method, which is based on comprehensive 'bottom-up' analyses of the activities of staff and other resources that are used

during those days. Medication prices will be based on the official list prices, including value added tax and increased by a standard prescription reimbursement for the pharmacist. The cost of production loss will be calculated according to the Friction Cost Approach.

Patient outcome analysis

The primary outcome measure in the economic evaluation is the difference in QALYs. The secondary effects are the delirium-free and coma-free days after treatment with haloperidol or placebo. As measuring QALYs in adult critically ill patients is not feasible at baseline, it is not possible to estimate the average number of QALYs for each treatment group. However, assuming that there is no difference at randomisation, it is possible to analyse the difference in quality of life at subsequent measurements in a multilevel regression model. This will enable us to calculate a difference in QALYs between the treatment groups over the total follow-up period, using linear intrapolation. HRQoL will be measured on t=1, 3, 6 and 12 months after randomization using the EQ-5D-5L instrument.

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Appendix 3: Haloperidol SPC

See this weblink: https://db.cbg-meb.nl/IB-teksten/h03185.pdf

for occurrences only

Appendix 4: (Semi-) structured review of literature on efficacy and adverse events of haloperidol for delirium in adult critically ill patients

1. Haloperidol as a treatment for ICU delirium

Systematic review of randomised placebo-controlled trials assessing haloperidol for treatment of ICU delirium

Method: A biomedical Information Specialist (BIS) of the Erasmus Medical Center library performed a systematic search aimed at controlled studies on haloperidol for ICU delirium combining the subjects: delirium, ICU and haloperidol, or equivalent terms (see: Appendix for details). No distinction was made in the search between treatment or prevention trials.

Review: Since focus of the EuRIDICE study is on a haloperidol versus placebo comparison, the study selection for this summary is also focused on placebo-controlled haloperidol trials for the treatment of ICU delirium. Systematic reviews from the systematic search are used as a crosscheck to confirm completeness or provide additional insights. The search (total of yielded only 1 study. The MIND trial (2010) was a randomised placebo controlled feasibility, efficacy and safety trial of antipsychotics for ICU delirium in adult mechanically ventilated medical and surgical patients (1). It included three treatment arms (haloperidol, n=35; ziprasidone, n=30 and placebo, n=36) and used a well thought out design (excluding demented patients with a validated tool for cognitive dysfunction, using CAM-ICU as a validated screening tool, a clear protocol with regard to QTc prolongation and study drug dosing, measuring extrapyramidal symptoms with a validated scale and with number of days alive without delirium and coma as the primary outcome (indicating total burden of brain dysfunction, since only assessing delirium days may result in increased coma days and less delirium days being regarded as a – false – improvement). The study used oral haloperidol, no clear sedation protocol aimed at light sedation and crossover antipsychotics were allowed but discouraged. No clear differences were found in the three groups with regard to the primary outcome. Mean haloperidol dose was 15 mg a day but QTc prolongation and extrapyramidal symptoms did not differ between treatment groups. Other medications in this small trial did not differ between groups (propofol, opiates, benzodiazepines). It was concluded that a larger trial would be safe and feasible.

Overview of most recent guidelines' statements on haloperidol as treatment for ICU delirium Method: Pubmed search on published guidelines including ICU delirium and containing information on

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haloperidol. Search terms: guideline, delirium, ICU.

Review: Three recent guidelines were retrieved (2-4). In a Danish guideline (2015) no evidence is stated for pharmacological management(2). A German guideline (2015) advocates symptom-based therapy when delirium screening is positive with haloperidol as a first choice in case of delirium associated with psychotic symptoms only. The "Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit" (2013)(3) advocate avoiding 'antipsychotics' when risk of torsades de pointes or is present or either baseline QT prolongation or concomitant QT prolonging medication is used. It states that there is no evidence that haloperidol decrease delirium duration, which was perceived as the most relevant issue to address with regard to haloperidol treatment of ICU delirium.

Cochrane review(s)

Method: Search on Cochrane (http://www.cochranelibrary.com) for reviews with search term: 'delirium', does not elicit any results pertaining to pharmacological treatment of delirium nor haloperidol.

Review: no Cochrane reviews exist on (ICU) delirium and it's pharmacological management.

On-going trials

Method: A search for 'haloperidol' and 'delirium' in the following online trial databases (and including ICU patients); www.trialregister.nl (0 trials); www.clinicaltrials.gov (4 trials).

Review: Four trials were retrieved from www.clinicaltrials.gov. One trial ('Haloquet') was not a truly placebo controlled trial because haloperidol was allowed ('as needed') in the placebo group and was last updated in 2013 but not published. It consisted of three treatments arms (also quetiapine) and aimed to include a total of 45 patients (and should thus be considered a pilot trial and not an efficacy trial). A second trial enrolled 40 patients and was completed in 2011 but not published. A third trial was a phase-2 safety/efficacy study enrolling 20 patients, last updated in 2007 and not published. The fourth trial ('The modifying the impact of ICU-associated neurological dysfunction-USA [MIND-USA] study') is currently recruiting (last verified May 2016 on September 14th). It is a multi-center double blind placebo-controlled trial aiming to enrol 561 patients in three treatment arms: haloperidol, ziprasidone and placebo, by the same research group that did the MIND trial. It includes cognitive and

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psychological follow-up at 12 months and is estimated to be completed July 2019. Maximum dose of haloperidol amounts to 10 mg IV q12 hours. Trial design is similar to the EuRIDICE trial, except for the patient experiences and perspective, and the fact that only patients on mechanical ventilation or in shock are included (i.e. the sickest ICU patients). The study protocol has not been published in a peerreviewed journal.

2. Haloperidol to prevent ICU delirium

Systematic review of randomised placebo-controlled trials assessing haloperidol for prevention of ICU delirium; including information from guidelines and Cochrane reviews

Method: A biomedical Information Specialist (BIS) of the Erasmus Medical Center library performed a systematic search aimed at controlled studies on haloperidol for ICU delirium combining the subjects: delirium, ICU and haloperidol, or equivalent terms (see: Appendix for details).

Review: the focus of this section is on randomised placebo-controlled prevention trials of haloperidol for ICU delirium. Three trials were retrieved. One trial included post-operative generally non-critically ill patients (5) and was not further considered for this review. The Hope-ICU trial (2013)(6) was a prophylactic study of haloperidol (2.5mg IV q8h, n=71) versus placebo (n=70) in adult mechanically ventilated ICU patients. The primary end-point of delirium (assessed with CAM-ICU) and coma free days did not differ between groups (5 days in both), but there was a 21% crossover rate with haloperidol in the placebo group. Secondary clinical endpoints such as length of stay at ICU or mortality did not differ but the trial was not powered on these outcomes. Another trial (2016)(7) including mechanically ventilated patients (n=68) with 'subsyndromal' delirium (=an Intensive Care Delirium Screening Checklist [ICDSC] score of 1-3 on a scale of 8, where 4 or more is compatible with delirium) used haloperidol 1mg IV q6h but did not find lower rate of progression to full delirium.

3. Haloperidol: adverse events versus treatment effects in the few available trials

The adverse events associated with haloperidol in the three aforementioned (small) trials (one treatment and two prevention trials) did not include QTc prolongation (with a threshold of >500 ms). In the Hope-ICU trial more opiates and sedatives were administered in the placebo-group but alfa-2

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agonists were not clearly protocolled, more agitation was present and 26% versus 11% antipsychotics' use in the placebo group. The subsyndromal delirium trial similarly found more agitation in the placebo group.

4. Healthcare perspective

A cost-effectiveness analysis of the Hope-ICU trial found that delirium increased cognitive dysfunction at 6 months and reduced quality of life, suggestive of potential cost-effectiveness of haloperidol (8).

5. Added value of the EuRIDICE trial

Based on this review of available pertinent literature after a thorough BIS-supported systematic search, the proposed trial in this grant application is expected to have important potential additional value:

The indication of haloperidol for ICU delirium will be delineated more clearly by this trial: does it decrease ICU brain dysfunction, associated long-term cognitive, functional and psychological outcomes? Is the intervention cost-effective? Are adverse events associated with haloperidol indeed concerning or actually negligible? Or: has haloperidol become obsolete, now that alternatives have been incorporated into clinical practice, mainly the atypical antipsychotics and alpha-2 agonists (dexmedetomidine and clonidine)? The EuRIDICE trial has a very strong potential to answers all of these questions.

A similar trial as EuRIDICE in the United States is on-going. However, US-based delirium research may not necessarily translate to European/Dutch settings as has been shown before (9), which justifies performing a second large multicentre clinical trial. Moreover, evidence on the pharmacological treatment of delirium is needed because of the lack of trials to date, and the level of evidence and generalizability of the efficacy findings for haloperidol will increase with a second trial. Third, cost-effectiveness of the intervention will be assessed from a healthcare and societal perspective and family and patient experiences will be investigated as important secondary outcomes. Further, we aim to include all critically ill patients, and not just the sickest, i.e. those on mechanical ventilation or in shock.

Existing guidelines and systematic reviews will have to be adapted on the basis of the results this proposed trial.

Acknowledgements:

Gerdien B. de Jonge (MSc), biomedical information specialist, Medical Library, Erasmus MC, is kindly

acknowledged for her help in assembling the databases for the systematic review.

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Appendix 5: Drug Accountability

The study drug will be obtained from the hospital pharmacy of each participating ICU. The research nurse of each participating ICU will record the number of the box with study drug for each patient in the CRF.

The research nurse of each participating ICU is responsible for retrieving the boxes with study drug. The amount of vials in the boxes will be counted for each patient and will be noted in the CRF. The research nurse will return unused drug to the hospital pharmacy. The hospital pharmacy will destroy the vials with study drug and will also record this (double administration).

The pharmacist or another appropriate individual who is designated should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, problems and irregularities during injection, the maintenance of the blinding, and the return to the pharmacy of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial patients (if applicable). Investigators should maintain records that document adequately that the patients were provided the doses specified by the protocol and reconcile all investigational product(s).

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Appendix 6: Example of the patient consent form

Subject information and consent form for participation in medical scientific research

Effectiveness of haloperidol for the treatment of acute confusion (delirium) in critically ill patients

<u>"Efficacy of halopeRI</u>dol to decrease the burden of <u>D</u>elirium <u>In adult Critically ill</u> pati<u>Ents (EuRIDICE)</u>: a prospective randomised multi-center double-blind placebocontrolled clinical trial"

(note: this Patient Information Letter is a translated version of the original Dutch document. It was Google translated and checked for readability by the study PI and coordinator)

Introduction

Dear Sir / Madam,

You receive this letter because you have been admitted to the Intensive Care Unit and have a chance (about 30%) of developing a delirium (sudden confusion) during admission. We ask you to participate in a medical-scientific study. Participation is voluntary. Your written permission is required to participate. Before you decide whether you want to participate in this study, you will receive an explanation of what the study entails. Please read this information carefully and ask the researcher if you have any questions. You can also ask the independent expert mentioned at the end of this letter for additional information. You can also discuss it with your partner, family or friends.

Further information about participating can be found in the attached brochure "Medical scientific research: general information for the test subject".

1. General information

This research was set up by Erasmus MC Rotterdam and is carried out by doctors and nurses in various hospitals in the Rotterdam region. This study requires a total of 742 subjects from different hospitals in the Rotterdam region. Erasmus MC's medical ethics review committee has approved this study. General information about the approval of research can be found in the brochure "Medical scientific research: general information for the test subject".

2. Purpose of the study

The aim of this study is to examine how safe and effective the drug haloperidol is for the treatment of acute confusion (delirium) in patients admitted to the Intensive Care Unit (ICU).

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Haloperidol has been widely used for many years to treat delirium in ICU patients. However, whether haloperidol can reduce delirium once it has occurred has never been properly investigated. We therefore compare the effects of haloperidol with a placebo. A placebo is a drug without an active substance, a "fake" drug.

3. Background of the study

Delirium (sudden confusion) is a common problem in patients on an ICU. Delirium is associated with an increased risk of death, memory and thinking disorders and a reduced general condition in patients who leave the ICU. A common drug used to treat delirium in ICU patients is haloperidol. This medicine can have a beneficial effect on sudden anxiety and delusions (hallucinations), which often occur with delirium, but can also have side effects. The advantages and disadvantages of treatment with haloperidol have never been properly investigated in a so-called randomized-controlled study.

4. What it means to participate

Examination of eligibility

First we determine whether you can participate. We ask you or your close family about possible memory complaints indicating cognitive dysfunction before your admission to the ICU. When a pregnancy is possible, a pregnancy test is done. If you have memory problems that require further investigation or if you are pregnant, we will tell you and you cannot participate in the study. If you do not want to know if you are pregnant, you cannot participate in this study.

Sometimes during the examination of eligibility or follow-up study we find memory complaints or anxiety or depression complaints that require further medical examination. We will always share these test results with you. Further management of any test results indicating memory issues, anxiety etc, will be done through your own GP. The costs are covered by your own insurance.

Treatment

If you give permission to participate in this study and develop a delirium during admission to the ICU, study medication will be started. We will treat you with study medication for a maximum of 2 weeks. Half of the subjects receive the active agent (haloperidol), the other half the fake agent (placebo). Random selection determines whether you will receive haloperidol or placebo. You, your close relative or family member and all caregivers, such as nurses and the researcher, do not know which group you are in. If it is necessary for your health, it can be looked up.

General information can be found in the brochure "Medical scientific research: general information for the test subject".

Visits and measurements

Data will be collected for the study in the first two weeks. A description of the measurements made for this can be found in Appendix C.

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For the examination, you will need to come to the hospital twice in 12 months after discharge to accurately test for memory and thinking disorders. A visit takes about 1.5 hours. If it is difficult for you to visit the hospital, we will try as much as possible to visit you at your home for the tests. You will also be sent questionnaires by post after discharge from the hospital, after 1, 3, 6 and 12 months after the ICU admission. The questions are about your experiences with and memories of the delirium and ICU admission, how fit you are and what physical limitations there may be. We also send questionnaires to your family member that record how they experienced your delirium and how they experience caring for you. See appendix C for a schedule with an overview and explanation of the visits and measurements.

Different from usual care

If you decide to participate, you will be randomized and you will receive either haloperidol ór no haloperidol, but will be treated with other drugs to decrease delirium symptoms. These agents other than haloperidol are already used as standard care in the ICU and are also effective against the complaints associated with delirium (such as severe anxiety or delusions or hallucinations - i.e. seeing things that are not there, which is sometimes frightening). The other treatments are the same between both groups. After ICU admission, the follow-up is more extensive compared with usual care because the tests of memory and fitness are not routine. If you do not participate in the study, you will receive routine medication and this is usually the treatment with haloperidol in this hospital.

5. What is expected of you

In order for the research to run smoothly, it is important that you adhere to the following agreements.

The agreements are that you:

- do not participate in any other medical scientific research in which a treatment is tested.
- show up at appointments for follow-up visits.

It is important that you contact the researcher:

- if you no longer wish to participate in the study.
- if your contact details change.

Pregnancy

Women who are pregnant or breastfeeding cannot participate in this study. Treatment with haloperidol can have consequences for an unborn child. This mainly concerns movement disorders, such as muscle stiffness at birth, but it is currently insufficiently known whether haloperidol is entirely safe. A pregnancy test will be performed, so that it can be established with certainty that you are not pregnant and can safely participate in the study.

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6. Possible side effects / complications

Haloperidol may cause side effects / adverse effects.

The most common disadvantages of haloperidol:

- slowing of nerve conduction in the heart, which can lead to arrhythmias
- muscle stiffness
- some drowsiness
- mild drop in blood pressure

Rare side effects are:

- muscle breakdown and high fever (so-called "neuroleptic malignant syndrome")
- serious heart rhythm disorders in which the heart can (temporarily) stop.

The researchers consider the chance of unknown adverse effects / side effects of haloperidol to be virtually nihil, since haloperidol has been used for a long time and all side effects of this drug are well known.

Not receiving haloperidol (placebo) could also have adverse effects.

The possible disadvantages of not giving haloperidol are:

- more restlessness / agitation
- more delusions

When you become restless or suffer from delusions in delirium, other drugs can be given that also work well against anxiety and delusions. The side effects of these other medications are known and usually mild, including slowing of the heart rhythm and drop in blood pressure.

Measurements

The management during admission to the ICU are in accordance with normal practice and do not place an additional burden on you. After discharge, you will be asked to complete questionnaires and tests will be taken during a hospital visit or at home. These tests are not painful.

7. Possible advantages and disadvantages

It is important that you carefully weigh the possible pros and cons before you decide to participate.

Haloperidol can reduce the symptoms of delirium and shorten its duration, and reduce the long-term adverse effects (cognitive complaints and your general functional status), but this is not certain. At any time during treatment with study medication, delirium symptoms may recur or worsen. This does not directly mean that you are in the placebo group, because delirium can also persist despite treatment with haloperidol.

Disadvantages of participating in the study may include:

- Possible side effects of the study medicine (haloperidol) or not receiving the study medicine (placebo)

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	 Possible side effects of other medications given during the study period to reduce anxiety and hallucinations 		
	 Possibly confronting questions about your functioning during and after discharge from the hospital. 		
	- Visits to the hospital or home visits, telephone interviews or questionnaires sent can be a burden.		
	Participation in the study also means:		
	- That you will have to spend extra time;		
	- That (extra) tests are done;		
	- That you have to adhere to agreements for the best result of the research;		
	All these matters are described above under points 4, 5 and 6.		
	8. If you do not want to participate or want to quit the study		
	You should decide for yourself whether you want to participate in the study. Participation is		
	voluntary. If you do not want to participate, you will be treated for delirium in the usual way		
	according to the applicable procedures and protocols. The researcher can tell you more		
	about the treatment options available and their advantages and disadvantages. There is a		
	website with information about the treatment of delirium and the study: https://icudelirium.nl. If		
	you do participate, you can always change your mind and stop, even during the study. You		
	will then be treated for delirium in the usual way. You don't have to say why you quit.		
	However, you must report this immediately to the researcher. The data collected up to that point will be used for the investigation		

If there is new information about the study that is important to you, the researcher will let you know. You will then be asked if you want to continue to participate.

9. End of the investigation

Your participation in the study stops if:

- all visits are over (according to the schedule / as described under point 4) •
- you choose to quit
- the researcher thinks it is better for you to quit
- Erasmus MC, the government or the assessing medical ethics review committee decides to stop the research.

The whole study is finished when all participants have been treated and have been followed for the procedures for this study.

After processing all data, the researcher will inform you about the main results of the research. The investigator can also tell you whether you have had haloperidol or the placebo. If you do not want this, you can tell the investigator. The researcher then is not allowed to tell you.

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10. Use and storage of your data

For this research it is necessary that your medical and personal data are collected and used. Each test subject is given a code that will appear on the data. Your name and other personal data that can directly identify you are omitted.

Your data

All your data remains confidential. Only the researchers working in your hospital know which code you have. We will send the data on to the coordinating investigator of the study, but only with that code, never by name. The key for the code remains with the local investigator. Also in reports about the research only that code is used.

Some people are allowed to view your medical and personal data. This is to check whether the research has been carried out properly and reliably. General information can be found in the brochure "Medical scientific research: general information for the test subject". People who can view your medical data are: members of the research team, the safety committee that monitors the investigation, an inspector who works for the client (Erasmus MC), the Health Care Inspectorate. The privacy of your personal data is always maintained. By signing the declaration of consent, you consent to the collection, storage and access of your medical and personal data.

Use of data on a later point

The researcher will keep your data for 15 years. We may use the data to do additional analyses for the study. This concerns research on delirium. You can indicate whether you agree with this on the consent form. You can always withdraw this permission. If no permission is given, you cannot participate in the study.

This research is also included in a public overview of medical scientific research, namely <u>www.trialregister.nl</u>. This website does not contain information that can be traced back to you as a person. However, the website can show a summary of the results. You can find this research under "EuRIDICE trial". General information about the registration of studies can be found in the brochure "Medical scientific research: general information for the subject".

11. Insurance for test subjects

Everyone participating in this study is insured. The insurance covers damage from the investigation. Not all damage is covered. Appendix B provides more information about the insurance. It also states who can report the damage.

12. Inform GP

We always send your doctor a letter to let them know that you are participating in the study. The details of the tests taken after admission to the Intensive Care Unit are secret. If you wish, or if the researcher deems it necessary, these data can be shared with the GP.

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13. Fee for Participation

The additional tests for the study cost you nothing. You will not be paid for participating in this study. You will receive a compensation of € 22 per visit for your (extra) travel costs and a € 5 lunch allowance per visit. You will not be reimbursed for a home visit.

14. Do you have any questions?

If you have any questions, please contact Dr. M. van der Jagt, principal investigator, or L. Smit, physician researcher. For independent advice on participation in this study, please contact the independent physician Dr. Dinis Dos Reis Miranda, anesthetist intensivist. He knows about this research, but is not involved in its implementation.

It is best to contact the complaints committee of Erasmus MC in case of complaints. All information can be found in Appendix A: Contact details.

15. Signing of consent form

When you have had enough time to consider participation, you will be asked to decide whether to participate in this study. If you give permission, we will ask you to confirm this in writing on the accompanying declaration of consent. By your written permission, you indicate that you have understood the information and that you agree to participate in the study. The signature sheet is kept by the investigator. You will receive a copy or a second copy of Revenues on the second this declaration of consent.

Thank you for your attention.

NL62689.078.17. ZonMw project number: 848041001. Haloperidol for IC delirium

Subject information for patients

16. Annexes to this information

A. Contact details

- B. Insurance information
- C. Schedule of investigative actions
- D. Consent form test subject
- E. Brochure "Medical scientific research. General information for the subject (version March
- 2017) (to be supplied separately)

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NL62689.078.17. ZonMw project number: 848041001. Haloperidol for IC delirium Subject information for patients					
Appendix A: Contact details Erasmus Medical Center					
Principal Investigator	Erasmus Medisch Centrum				
Dr. M. van der Jagt, ner	urologist-intensivist				
Via the general telepho	ne number Erasmus MC	: 010- 704 07 04			
Researcher Erasmus	Medisch Centrum				
Lisa Smit	: physician researcher				
Via the general telepho	ne number Erasmus MC	: 010- 704 07 04			
Or via the research team	m				
Independent physicial	n Erasmus Medisch Centrum				
Dr. Dinis Dos Reis Miranda, anesthetist-intensivist					
Via the general telepho	ne number Erasmus MC	: 010- 704 07 04			
Research team Erasm	us Medisch Centrum				
Ditty van Duijn	: Research Coördinator Intensive Care				
Patricia Ormskerk	: Research Coördinator intensive Care				
Alicija Vileito	: Research Coördinator Intensive Care				
Can be reached during	office hours on:	: 010-703 51 42			
Complaints Committe	e				
Erasmus Medisch Cent	rum				
Can be reached on:		: 010-703 31 98			

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Appendix B: Information about the insurance

The sponsor insures everyone who participates in this study. The insurance covers damage due to participation in the study. This applies to damage during the investigation or within four years after its end. You must report damage to the insurer within those four years.

The insurance does not cover all damage. At the bottom of this text is briefly mentioned what damage is not covered.

These provisions are set out in the Decree on compulsory insurance for medical research involving human subjects. This decision can be found on www.ccmo.nl, the website of the Central Commission for Human Research (see 'Library' and then 'Laws and regulations').

In the event of damage, you can contact the insurer directly.

	The insurer of the study is:				
	Name	: CNA Insurance Company Limited			
	Address	: Strawinskylaan 703			
		: 1077 XX Amsterdam			
	Phone number	: 020 – 573 72 74			
	E-mail	: Esther.vanherk@cnahardy.com			
	Polis-number	: HCCD0416C			
	Contactperson	: Esther van Herk			
The insurance covers					
- € 650,000 per subject					
	- € 5,000,000 for the entire study				
	- € 7,500,000 per insurance year				

- -€ 650,000 per subject
- € 5,000,000 for the entire study
- € 7,500,000 per insurance year

The insurance does not cover the following damage:

- damage due to a risk about which you have been informed in the written information. This does not apply if the risk is more serious than anticipated or if the risk was very unlikely;
- damage to your health that would have occurred even if you had not participated in the study;
- damage caused by not (fully) following directions or instructions;
- damage to your offspring, as a result of a negative effect of the research on you or your offspring;
- damage caused by an existing treatment method when investigating existing treatment methods.

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Appendix C - Measurements overview

During treatment with the study medication, a heart film will be made daily to determine whether the conduction in the heart is good, and muscle stiffness will be examined. You will also be asked every morning how you slept. In addition, delirium will be assessed daily. The attention is examined and the general condition is examined a few months after the IC admission.

The table below shows which normal care and which extra care you receive in the context of the ICU examination. The table also shows the moments you will be asked to visit the hospital (if desired and feasible for you and us, we will strive for home visits instead of hospital visits) or to complete questionnaires. The tests for memory and thinking take about 1 hour. The table shows the approximate minutes to complete the questionnaires (In brackets).

Moment (months)	Usual care on the ICU	Extra care during the study	Cognitive tests	Experiences related to delirium	General condition
Once before participation		 Questionnaire about your memory Pregnancy test (if applicable) 			
During study at the ICU	- Delirium assessm ent (3x/day)	 EKG (1x/day) Test muscle stifness (1x/day) Sleep quality (1x/day) 			
0 (discharge hospital)				Participant: Questionnaires (30) Proxy/family: Questionnaire (2)	
1					Questionnaires (30)
3			Hospital or home visit	Participant: Questionnaires (35) Proxy/family: Questionnaire (12)	Questionnaires (40)
6					Questionnaires (30)
12			Hospital or home visit		Questionnaires (40)

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Appendix D: Consent form test subject

Effectiveness of haloperidol for the treatment of acute confusion (delirium) in critically ill patients

- I have read the information letter. I was also able to ask questions. My questions have been answered sufficiently. I had enough time to decide whether to participate.
- I know that participating is voluntary. I also know that I can decide at any time not to participate or to stop the research. I don't have to give a reason for that.
- I give permission to inform my GP that I am participating in this study and to inform them about test results of memory and thinking ability and possible anxiety or depression complaints, if the researcher deems this necessary.
- I know that some people can access my data. Those people are listed in this information letter.
- I consent to the collection and use of my data in the manner and for the purposes stated in the information letter.
- I give permission to keep my data at the research location for 15 years after this research.
- I know I should not be pregnant during the study (if applicable)
- I declare to Declare to
 - □ **not give** permission to contact me again after this investigation for a follow-up investigation

- I □ do

□ **do not** want to be informed about which treatment I had or in which group I was.

- I want to participate in this study.
- Name:

Signature:

Date: __ / __ / __
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NL62689.078.17. ZonMw project number: 8 Subject information for patients	848041001. Haloperidol for IC delirium
I declare that I have fully informed th	nis subject about the said study.
If during the research information be subject, I will inform him / her in goo	comes known that could influence the consent o d time.
Name researcher (or its representation	ive):
Signature:	Date: / /
Additional information is provided by Name: Function: Signature:	/ (if applicable): Date: / /
* Strike out what does not apply.	
The subject will receive a full informa	ation letter, along with a copy of the signed const

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Appendix 7: Unblinding Procedure

The study treatment will be unblinded after Database Lock. While the safety of patients should always take priority, maintenance of blinding is crucial to the integrity of a double-blind trial. Before this planned unblinding, the blinding for a specific patient should only be broken when information about the patient's protocol treatment is considered necessary to manage Serious Adverse Events (emergency unblinding). Unblinding procedures should preferably be initiated only after consultation of the principal investigator/coordinating investigator or his/her representative. To initiate an emergency unblinding the pharmacy in charge of the randomisation list should be contacted. Breaking the blinding on a patient will be logged and reported to the coordinating Investigator within 24 hours following the unblinding procedure, using the Emergency Unblinding Form. It is considered a major protocol violation, after which the patient goes off protocol treatment (if applicable).

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

			Page
		Reporting Item	Number
Administrative information			
Title	<u>#1</u>	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	<u>#2a</u>	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	<u>#2b</u>	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	<u>#3</u>	Date and version identifier	2
Funding	<u>#4</u>	Sources and types of financial, material, and other support	22
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1 2 3 4 5	Roles and responsibilities: contributorship	<u>#5a</u>	Names, affiliations, and roles of protocol contributors	1, 20
6 7 8 9 10 11	Roles and responsibilities: sponsor contact information	<u>#5b</u>	Name and contact information for the trial sponsor	1,2
13 14 15 16 17 18 19 20 21 22	Roles and responsibilities: sponsor and funder	<u>#5c</u>	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22
22 23 24 25 26 27 28 29 30	Roles and responsibilities: committees	<u>#5d</u>	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14
31 32	Introduction			
33 34 35 36 37 38 39	Background and rationale	<u>#6a</u>	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-5
40 41 42 43 44	Background and rationale: choice of comparators	<u>#6b</u>	Explanation for choice of comparators	3-5
45 46	Objectives	<u>#7</u>	Specific objectives or hypotheses	4
47 48 49 50 51 52 53				
49 50 51 52 53 54	Trial design	<u>#8</u>	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
49 50 51 52 53 54 55 56	Trial design Methods:	<u>#8</u>	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
49 50 51 52 53 54 55 56 57 58 59 60	Trial design Methods: Participants,	<u>#8</u>	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4

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1 2	interventions, and outcomes			
3 4 5 6 7 8 9	Study setting	<u>#9</u>	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
10 11 12 13 14 15 16	Eligibility criteria	<u>#10</u>	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-6
17 18 19 20 21	Interventions: description	<u>#11a</u>	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10
22 23 24 25 26 27 28	Interventions: modifications	<u>#11b</u>	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9-12
29 30 31 32 33	Interventions: adherance	<u>#11c</u>	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	11
35 36 37	Interventions: concomitant care	<u>#11d</u>	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11-12
38 39 40 41 42 43 44 45 46 47 48 49	Outcomes	<u>#12</u>	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-9
49 50 51 52 53 54 55	Participant timeline	<u>#13</u>	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7-9
56 57 58 59 60	Sample size	#14 peer revie	Estimated number of participants needed to achieve study objectives and how it was determined, including ew only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	17

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1 2 3			clinical and statistical assumptions supporting any sample size calculations	
4 5 6 7	Recruitment	<u>#15</u>	Strategies for achieving adequate participant enrolment to reach target sample size	12
9 10 11 12 13	Methods: Assignment of interventions (for controlled trials)			
14 15 16 17 18 19 20 21 22 23 24 25	Allocation: sequence generation	<u>#16a</u>	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12-13
26 27 28 29 30 31	Allocation concealment mechanism	<u>#16b</u>	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12-13
32 33 34 35 36	Allocation: implementation	<u>#16c</u>	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12-13
37 38 39 40 41 42	Blinding (masking)	<u>#17a</u>	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12-13
43 44 45 46 47	Blinding (masking): emergency unblinding	<u>#17b</u>	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12-13
48 49 50 51 52 53 54	Methods: Data collection, management, and analysis			
55 56 57 58 59 60	Data collection plan	<u>#18a</u> Deer revie	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate w only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	7-9

			BMJ Open	Page	e 58 of 5
1 2 3 4 5 6 7			measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol		
8 9 10 11 12 13 14	Data collection plan: retention	<u>#18b</u>	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13-14	Protected by
15 16 17 18 19 20 21 22	Data management	<u>#19</u>	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12, 15	r copyright, including fc
23 24 25 26 27 28 29	Statistics: outcomes	<u>#20a</u>	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16	Enseignement S or uses related to te
30 31 32 33	Statistics: additional analyses	<u>#20b</u>	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16-17	uperieur (/ xt and data
34 35 36 37 38 39 40	Statistics: analysis population and missing data	<u>#20c</u>	Definition of analysis population relating to protocol non- adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14	ABES) . a mining, Al training,
41 42	Methods: Monitoring				and s
43 44 45 46 47 48 49 50 51 52 53	Data monitoring: formal committee	<u>#21a</u>	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14	similar technologies.
55 55 56 57 58 59 60	Data monitoring: interim analysis	<u>#21b</u> peer revie	Description of any interim analyses and stopping guidelines, including who will have access to these w only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	16-17	

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1 2			interim results and make the final decision to terminate the trial	
3 4 5 6 7 8 9	Harms	<u>#22</u>	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15-16
10 11 12 13 14 15	Auditing	<u>#23</u>	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
16	Ethics and			
17 18 19	dissemination			
20 21 22	Research ethics approval	<u>#24</u>	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	17
23 24 25 26 27 28 29 30 31	Protocol amendments	<u>#25</u>	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	17
32 33 34 35 36	Consent or assent	<u>#26a</u>	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18
37 38 39 40 41	Consent or assent: ancillary studies	<u>#26b</u>	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
42 43 44 45 46 47 48	Confidentiality	<u>#27</u>	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18
49 50 51 52	Declaration of interests	<u>#28</u>	Financial and other competing interests for principal investigators for the overall trial and each study site	22
53 54 55 56 57 58	Data access	<u>#29</u>	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	-
59 60	For	peer revie	w only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

1 2 3 4 5	Ancillary and post trial care	<u>#30</u>	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
6 7 8 9 10 11 12 13	Dissemination policy: trial results	<u>#31a</u>	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	3
14 15 16 17	Dissemination policy: authorship	<u>#31b</u>	Authorship eligibility guidelines and any intended use of professional writers	-
18 19 20 21	Dissemination policy: reproducible research	<u>#31c</u>	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
22 23	Appendices			
24 25 26 27	Informed consent materials	<u>#32</u>	Model consent form and other related documentation given to participants and authorised surrogates	-
28 29 30 31 32 33	Biological specimens	<u>#33</u>	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA
34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 50 51 52 53 54 55 56 57 58 50	None The SPIRIT check License CC-BY-ND 3.0. tool made by the EQUA	dist is di This ch <u>TOR Ne</u>	astributed under the terms of the Creative Commons Attribut ecklist can be completed online using <u>https://www.goodrep</u> etwork in collaboration with <u>Penelope.ai</u>	tion orts
60	For	heerievie	w only - http://bhijopen.bhij.com/site/about/guidelines.xhtml	