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Title: Intranasal insulin for treatment of delirium in older hospitalised patients: study protocol for a randomised controlled trial

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Abstract

Introduction: Delirium is one of the most common conditions diagnosed in hospitalised older people and is associated with numerous adverse outcomes, yet there are no proven pharmacological treatments. Recent research has identified cerebral glucose hypometabolism as a pathophysiological mechanism offering a therapeutic target in delirium. Insulin, delivered via the intranasal route, acts directly on the central nervous system and has been shown to enhance cerebral metabolism and improve cognition in patients with mild cognitive impairment and dementia. This trial will determine whether intranasal insulin can reduce the duration of delirium in older hospitalised patients.

Methods and analysis: This is a prospective randomised, placebo-controlled, double blind study with 6 months follow up. One hundred patients aged 65 years or older presenting to hospital with delirium admitted under Geriatric Medicine will be recruited. Participants will be randomised to intranasal insulin detemir or placebo administered twice daily until delirium resolves, defined as Confusion Assessment Method (CAM) negative for two days, or discharge from hospital. The primary outcome measure will be duration of delirium using the CAM. Secondary outcome measures will include length of hospital stay, severity of delirium, adherence to treatment, hospital complications, new admission to nursing home, mortality, use of antipsychotic medications during hospital stay and cognitive and physical function at 6-months post-discharge.

Ethics and dissemination: This trial has been approved by the South Eastern Sydney Human Research and Ethics Committee. Dissemination plans include submission to a peer-reviewed journal for publication and presentation at scientific conferences.

Trial registration: ACTRN12618000318280

Strengths and Limitations:

- The study design is pragmatic, inclusive and representative of real-world older hospitalised patients who are often omitted from research due to multimorbidity.
- The results will add valuable insights into the neural mechanisms leading to delirium.
- Patients in this study will be followed up trained assessors daily for up to one-week post-discharge, however, assessment after one week is beyond the allocated resources for this trial.

Background

Delirium is common, with figures reporting 10-35% of older people are delirious on admission to hospital (prevalent delirium) and up to another 29% will become delirious during their admission (incident delirium) (1). It is characterised by sudden and fluctuating disturbances in cognition, attention and awareness (2). The sequelae of delirium are manifold and extend beyond the acute hospitalisation; increased mortality, new cognitive impairment, accelerated dementia, loss of independence and increased admission to nursing home(3, 4). In older patients, delirium is independently associated with a two-fold increase in mortality at 12 months (5). Longer duration and increased severity of delirium predict poorer outcomes in older patients (6).

Studies suggest that only 30% of incident delirium is potentially preventable with non-pharmacological multimodal intervention (7). Current management focuses on identifying and treating the underlying cause of delirium combined with non-pharmacological interventions to provide an optimal environment for brain recovery and reduce the risk of potentially avoidable complications such as falls and pressure injuries.

Pharmacological management is focused on symptomatic control with antipsychotics. However, evidence does not support the use of antipsychotics for delirium and a recent randomised controlled trial demonstrated worsening symptoms and increased mortality (8, 9). At this point in time there are no proven pharmacological interventions to prevent or manage delirium.

Delirium pathophysiology is poorly understood, although several hypotheses exist. These include neuroinflammation (10), neurotransmitter dysregulation (11), neuroendocrine dysregulation (12) and neural network dysconnectivity (13). As delirium is a complex and heterogeneous disorder, it is likely that several of these mechanisms may contribute to the development of delirium with varying effect depending on pre-existing patient vulnerabilities and the aetiology of the acute precipitant (14). However, regardless of the underlying cause, delirium presents in a recognisable and stereotyped manner (phenotypically hypoactive, hyperactive and mixed) and the hypothesis that a "final common pathway" may exist should not be disregarded.

Research has identified altered cerebral perfusion and metabolism as a feature of delirium. Delirious patients have higher cerebrospinal fluid (CSF) lactate and lower neuron-specific enolase suggesting suppressed aerobic metabolism during an episode of delirium (15, 16). Two studies have demonstrated cerebral glucose hypometabolism during delirium using fluorodeoxyglucose positron emission tomography (FDG-PET) (17, 18). Haggstrom et al have demonstrated a correlation between posterior cingulate cortex hypometabolism and attention as well as evidence of improved cortical glucose metabolism with resolution of delirium (17). Neuroimaging studies using a variety of modalities have demonstrated reduced cerebral perfusion, decreased cerebral oxygenation and abnormal cerebral autoregulation during an episode of delirium (19, 20). As cerebral blood flow and metabolism are closely coupled and considered to reflect synaptic activity(21), correction of perfusion and metabolism abnormalities may improve clinical outcomes in delirium.

It is now well established that the brain is an insulin sensitive organ; insulin receptors are widely expressed in the brain, with greatest saturation in the corticolimbic structures (22). Insulin enhances learning and memory by modulating neuronal growth, metabolism, plasticity and cholinergic function (22, 23).

The role of glucose metabolism in the pathogenesis of neurodegenerative disease is a growing area of research (24). Mild Cognitive Impairment (MCI) and Alzheimer's Dementia (AD) have been

characterised as states of brain-specific insulin resistance and deficiency sometimes called “type 3 diabetes” (25). Patients with early stage AD demonstrate pronounced insulin and insulin-like growth factor deficiency and resistance which progress with severity of neurodegeneration (22). Administration of intravenous (IV) insulin while maintaining fasting serum glucose levels improves memory in patients with Alzheimer’s Disease (26). However, therapeutic administration of IV insulin is not feasible or safe due to the substantial risk of systemic hypoglycaemia.

The intranasal route of delivery provides a non-invasive and safe means of transporting insulin to the brain. A recent systematic review identified seven studies (total, N =293) examining the effect of intranasal insulin on MCI or AD, of which six demonstrated significant improvements in verbal memory (27). Positive outcomes in functional status were also observed (28-30). Improvements in attention, visuospatial memory and executive function have also been demonstrated in other populations (31-33).

One pilot trial has assessed the effect of intranasal insulin on delirium prevention in a cohort of 21 older cardiothoracic surgical patients (34). The incidence of postoperative delirium was lower in the intranasal group (18% vs 40%) although the result was not statistically significant, likely due to the small sample size. No serious adverse events were reported (35).

Given that intranasal insulin improves cognition as well as cerebral perfusion and metabolism, this trial will investigate its potential role in treatment of delirium.

This randomised controlled trial will evaluate whether intranasal insulin, compared to placebo, can reduce the duration of delirium in older patients admitted under Geriatric Medicine.

Methods

Design

This is a single site, randomised, double-blind, placebo-controlled trial of 100 older people diagnosed with delirium on admission to hospital (prevalent delirium). Figure 1 gives an overview of study design.

This research will be conducted in accordance with the Declaration of Helsinki. The trial methods, protocol and consent procedures were approved by the South Eastern Sydney Human Research and Ethics Committee (HREC 16_320). As required by the New South Wales Guardianship act 1987 (part 5), New South Wales Civil and Administrative Tribunal, approval to conduct this clinical trial has also been obtained (case number 2017/00204946). The trial was registered in the Australian and New Zealand Clinical Trial Registry on 5 March 2018 (ACTRN12618000318280).

Population

The study population will comprise older people admitted under a Geriatrician at a large tertiary hospital in metropolitan Sydney, Australia. Potential participants must be a) diagnosed with prevalent delirium, b) receiving inpatient care on the Geriatric Medicine Wards, c) age > 64 years, d) have a consenting "person responsible" and e) be enrolled in the trial within 24 hours of admission to hospital. People with known cognitive impairment and dementia will be included.

Exclusion criteria include a) people who are haemodynamically unstable, b) have a predicted life expectancy of less than seven days as judged by the admitting geriatrician, c) have an allergy to insulin detemir formulation or d) a structural abnormality precluding the use of the nasal drug delivery device. People will also be excluded if consent is not obtained or they were previously

enrolled in the trial. Non-English-speaking patients who are unable to participate in cognitive assessments will also be excluded. The trial will not include patients with incident delirium.

Screening and Evaluation of delirium

Within the emergency department or on transfer to the Geriatric Medicine Ward, all patients age >64 years will be screened by nursing staff for delirium using the Confusion Assessment Method (CAM) (36, 37). Patients with delirium diagnosed by a Geriatrician or Advanced Trainee in Geriatric Medicine using the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition criteria (DSM V) will be considered for the trial (38).

Study team members will use the CAM to conduct daily delirium assessments between 12-2pm. All members of the study team will undergo formal training using the CAM. Bedside assessment will be supplemented by review of the medical records and collateral history from the patient's carer or ward staff where appropriate. The presence of delirium will be documented using the long form CAM (36). Delirium severity will be assessed using the Delirium Index (DI) (39). Delirium clinical subtype will be assessed using the abbreviated version of the Delirium Motor Subtyping Scale (DMSS-4) (40).

Interrater reliability using the CAM and DI will be assessed using Cohen's kappa coefficient based on twenty patient reviews (41).

Consent

Consent will involve conversations regarding the study risks, benefits and burdens between the researchers, patient and the "person responsible" (substitute decision maker according to the New

South Wales Guardianship Act 1987). To avoid a delay in initiation of the intervention, where a person responsible is unable to attend the hospital to sign the consent, an initial verbal consent may be granted (by phone) and written consent obtained as soon as possible.

Consent to remain in the trial will be obtained from the patient if capacity returns. Should the patient decline further involvement in the trial the researcher will ask the patient for consent to use trial data up until the time of withdrawal in the final analysis.

Consent will also be obtained for the collection and study of patient blood specimens.

Assessment over the study period

Table 1 highlights the measures to be undertaken at each pre-determined time point. Measurements will be taken daily while receiving the intervention. Patient assessment will also occur at discharge from hospital and 6 months post discharge.

In addition to routine blood tests, 20millilitres of blood will be taken from each patient and stored for later analysis, including the effect of Apolipoprotein E4 (APOE4) status on study outcomes. Specimens will be frozen and stored at -80 degrees Celsius in the University of New South Wales Lowy Biorepository.

Randomisation and blinding

Permutated block randomisation will be conducted with a block size of 4 and 25 blocks using a computer-generated algorithm. An independent clinical trials pharmacist will create the randomisation schedule which will be provided to the clinical trials pharmacy staff responsible for production and dispensing of the medication. Each vial of insulin or placebo will be labelled with a sequentially allocated randomisation number, which will become that patient's study number.

Participants, research and ward staff will be blinded to treatment allocation.

Intervention

Patients will receive 20 international units (IU) of long-acting insulin (detemir) or a placebo of normal saline intranasally twice daily at 8am and 8pm via a commercially available drug delivery device (ViaNase delivery device, Kurve Technology, Bothell, Washington). This device has been used successfully in previous trials of intranasal insulin in cognitive impairment (29, 30). The device will release 20IU insulin detemir or placebo intranasally via a small nose piece over a 40 second period. Patients will receive 20 seconds per nostril twice daily and during administration be instructed to breath normally through the nose.

Following intranasal administration, insulin enters the brain either through direct entry via the cribriform plate and the olfactory nerves or via specific receptors in the blood-brain barrier or a combination of the two (42). In 15-30 minutes, insulin peptides are detected within the cerebral cortex and hippocampus (43). Compared to the subcutaneous route, intranasal administration of insulin demonstrates an approximately 2000-fold increase in the $AUC_{brain:plasma}$ ratio, meaning at similar doses the intranasal route reaches comparable or increased brain insulin concentration but substantially lower plasma concentration (44).

The total daily dose of 40IU of insulin detemir is based on research by Claxton et. al demonstrating safety and efficacy in older patients with Alzheimer's dementia. In this trial, 60 patients with mild cognitive impairment or mild-to-moderate AD received either placebo, 20IU of insulin detemir, or 40IU of insulin detemir intranasally for 21 days. Participants receiving 40IU of insulin detemir demonstrated significant improvements in verbal and visuospatial working memory. No statistically significant effect was found in the 20IU detemir group. No treatment-related severe adverse events were reported (45).

Pre-prepared, spare vials and in-use devices will be stored between 2-8 degrees Celsius in the ward medication fridge.

The medication will be administered by ward registered nurses specifically trained for the trial. Insulin is considered a "schedule 4" drug meaning two nurses must check the prescription, patient identity and be present for drug administration. Nurses will record challenges regarding administration of the intervention, including partially received or omitted doses, in the electronic patient record which will be reviewed by trial staff daily.

The intervention will cease following two consecutive CAM negative days.

Cessation of treatment with the study intervention will also occur if:

- The patient is discharged from the hospital
- Patient or treating clinician requests discontinuation
- Unacceptable side effects from study medications (defined by National Cancer Institute Common Criteria for Adverse Events; Common Terminology Criteria for Adverse Events version 4.0)
- Participants who in the opinion of the investigator are not well enough to continue in the study
- Adverse events related to the study medicine are unacceptable to the participant/carer or clinician in charge e.g. symptomatic or severe hypoglycaemia (blood sugar level <3.0mmol/L)
- Treatment is deemed ineffective, defined as no improvement in delirium index over 7 days.

Patients withdrawn from the study will be included in statistical analysis on an intention-to-treat basis.

Safety

Studies have demonstrated that less than 3% of intranasally-delivered insulin is detectable in the serum and as a result intranasal insulin has a negligible risk of hypoglycaemia (27, 46). A systematic review on the safety of intranasal insulin included 38 studies (N=1092) and found no cases of hypoglycaemia or severe adverse events (47). The most commonly reported side effects were transient and local to the nasal area including nasal tingling and burning, less commonly rhinitis and nasal bleeding occurred.

Although the risk of hypoglycaemia is largely theoretical, blood glucose levels will be measured at baseline and four times daily during the study intervention (07:00, 13:00, 19:00, 22:00). As adequate and uninterrupted sleep is a core principle in delirium management and disturbed sleep can precipitate or exacerbate delirium, blood glucose levels will not be taken overnight.

Adverse events will be assessed daily through participant interview supplemented by review of the electronic medical record. Serious adverse events as defined by the International Conference on Harmonisation Guidelines for Good Clinical Practice will be reported in accordance with local ethics requirements. An independent data and safety monitoring board (DSMB) will oversee the study and meet after each twenty patients. Serious adverse events will be discussed with the lead investigator immediately and reported to the Human Research Ethics Committee (HREC) and trial DSMB within 24 hours.

Delirium is associated with a high in-hospital mortality rate, previously demonstrated to reach 35% in an older population (48). As such, a key role of DSMB will be to review all deaths and serious adverse events in detail to determine if the adverse event was in keeping with the natural history of the illness or could be attributed to the study intervention (49). Should concerns arise regarding patient safety the DSMB may request to unblind for decision making purposes.

There are two main scenarios which could prompt DSMB to request termination of the study. Firstly, if there are a significant number of serious adverse events possibly attributed to the intervention leading to patient safety concerns and secondly, significant benefit from the intervention. Should termination of the trial be requested, researchers would be unblinded and data analysis would occur. The HREC and participants would be informed the trial was stopped and reasons for termination given.

Outcomes

The primary and secondary outcomes are outlined in table 1. The primary outcome will be duration of delirium in days. Delirium assessment will be conducted daily from enrolment until delirium resolution, defined as two consecutive days (48hours) CAM negative. Patients discharged with delirium will be followed up daily for up to one week to assess for delirium resolution. Secondary outcomes will determine if intranasal insulin compared to placebo decreases acute length of hospital stay, reduces severity of delirium, reduces hospital complications, reduces new admission to nursing home, decreases mortality and decreases use of antipsychotic medications during an inpatient stay. Patients will be followed up at 6 months post-discharge to assess if intranasal insulin reduces mortality and preserves cognition and function. Adherence to the intervention will be measured by percentage of doses successfully administered.

Sample size

Power analysis (with 5% significance and 80% power) was performed using published data which shows the mean duration of delirium clustered at approximately 8 days in Geriatric medicine ward populations(50, 51). Power calculation shows reducing delirium duration by two days (from 8 days to

6 days) requires 36 in each arm for a total of 72 patients. Allowing for a 30% dropout rate, a total of 100 participants will be sought.

Statistical Analysis

Statistical analysis will be conducted using IBM SPSS Statistics software. An intention-to-treat approach will be adopted for all analyses and statistical significance assumed at the level of 5% ($P<0.05$). Baseline characteristics will be reported for the overall population and separately for each group.

The primary outcome, duration of delirium measured in days, will be analysed first with a Mann Whitney U test which has high statistical power (52) and then using survival analysis Cox proportional hazard method including dementia, nursing home status, severity of disease and comorbidity as covariates. Sensitivity analysis will be conducted using normality-improving data transformations or Gamma regression with a log link according to the distribution of the primary outcome. For the major secondary outcome, trajectory of delirium severity measured by the delirium index over time, a generalised linear mixed model will be used. Binary outcomes like mortality (in-hospital and at six months) and institutionalisation will be evaluated using a modified Poisson regression (53). A linear regression will assess possible preservation of function, measured by Barthel index (54) and modified Instrumental Activities of Daily Living (55), and for all other linear secondary outcomes. Bootstrapping will be applied if the models fail to satisfy the normality assumptions. For length of hospital stay, a log-linear or gamma regression with a log link will be implemented. The number of hospital complications and the use of antipsychotics during hospitalization will be reported.

Subgroup analysis stratifying by age, sex, dementia and APOE status will be conducted.

Data Management

Data will be collected by trained researchers and stored on a password protected database. One researcher will be responsible for data entry while another member of the study team will monitor the accuracy of data by cross-checking a random 10% sample of subjects.

Paper files of individual records will be stored in a locked cabinet in a secure location accessible to authorised members of the study team only. Electronic data will be entered in a de-identified format and stored on a password-protected secure server. The complete data set will be stored on the University of New South Wales Data Archive and will be made available at the completion of the trial on reasonable request.

Patient and public involvement

A public representative approved trial concept, design and consent procedures as part of the application to New South Wales Civil and Administrative Tribunal. Results of the trial will be published in biomedical journals and presented at international scientific conferences. Social media platforms will be used to inform the general public about the results. Authorship on publications related to this study will follow standard eligibility guidelines ensuring significant contribution.

Discussion

Delirium is a debilitating condition commonly affecting older people in hospital and for which there are no registered treatments. It has been consistently demonstrated that longer duration of delirium predicts worse outcomes, including higher mortality and new admission to residential aged care facility (6, 56). Although the pathophysiological mechanisms are incompletely understood, it is probable that an episode of delirium causes irreversible neuronal damage leading to sustained

cognitive and functional impairment (57), with prolonged delirium exposure leading to greater cerebral damage.

To date, there are no trials assessing intranasal insulin as a treatment for delirium, however, it could improve cognitive and clinical outcomes for delirious patients via a variety of mechanisms. Intranasal insulin increases cerebral perfusion (32, 58-60) and increases or maintains cerebral glucose metabolism on FDG-PET (61, 62). In young healthy adults and patients with type II diabetes mellitus, intranasal insulin enhances functional connectivity within the default mode network, an important centre for higher cognitive processes in which delirious patients demonstrate dysconnectivity (13, 63, 64). The hypothalamic-pituitary-adrenal (HPA) axis is also insulin responsive and following administration of intranasal insulin healthy populations demonstrate diminished saliva and plasma cortisol (31, 65). As aberrant HPA axis activity is hypothesised to contribute to delirium pathophysiology, modification of this pathway may also lead to improved outcomes (12).

We anticipate this trial will be pragmatic, inclusive and representative of real-world Geriatric medicine inpatients. As such, we will include patients with pre-existing dementia and those residing in residential aged care facilities. This vulnerable population is at highest risk for delirium yet commonly under-represented in therapeutic trials.

An important aspect of this study will be patient tolerability of an inhaled nasal solution twice daily. Ward registered nurses administering intranasal insulin will receive training in both administration and subsequent documentation of the intervention. We will report on adherence and patients will be analysed on an intention-to-treat basis.

As duration of delirium is perhaps the most clinically relevant outcome for both clinicians and patients, we have chosen this as the primary outcome for the trial. The mean duration of delirium in Geriatric medicine inpatients has been demonstrated to be 8 +/- 9 days, however, symptoms of delirium can persist for up to 12 months (50). We anticipate some patients, particularly those returning to high level care residential aged care facilities, will be discharged with delirium and this group will be

followed up daily for up to one week to assess for delirium resolution. Daily assessment after one week is beyond the allocated resources for this trial.

If found to be efficacious, this would lead to multicentre trials to confirm these findings. There would also be the opportunity to explore intranasal insulin in prevention of delirium and its role across settings, including in the intensive care and post-operative populations which also represent vulnerable patient groups.

Should the intervention reduce the duration of delirium the benefits to patients and their families could be significant, both in alleviating acute distress and longer-term negative sequelae of delirium. The treatment also has the potential to save significant financial resources related to both the acute treatment of delirium and the residual effects with regards to loss of independence and higher care needs after resolution of delirium. Finally, irrespective of the outcome, this trial will contribute to our understanding of the pathophysiological mechanisms of delirium particularly the role of impaired cerebral perfusion and metabolism.

Declarations

Ethics approval and consent to participate: The trial methods, protocol and consent procedures were approved by the South Eastern Sydney Human Research and Ethics Committee (HREC 16_320). As required by the New South Wales Guardianship act 1987 (part 5), New South Wales Civil and Administrative Tribunal, approval to conduct this clinical trial has also been obtained (case number 2017/00204946).

Consent for publication: Not applicable.

Availability of data and materials: Materials including data collection and consent forms can be accessed by contacting the corresponding author.

Competing interest: The authors declare that they have no competing interests.

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Author contributions: GC initiated the study and is the trial sponsor. AN, AM and GC designed the original protocol. JC and MR provided substantial input in study processes and logistics. BTu provided expertise in the area of Endocrinology. BTo provided extensive guidance on the statistical analysis. All authors contributed to the writing of the manuscript and approved the final version.

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Abbreviations: AD: Alzheimer's dementia; AUC: area under the curve; APOE: Apolipoprotein E; CAM: confusion assessment method; CSF: cerebrospinal fluid; DI: delirium index; DSM: Diagnostic and Statistical Manual of Mental Disorders; DSMB: data and safety monitoring board; FDG-PET: fluorodeoxyglucose positron emission tomography; HPA: hypothalamic-pituitary-adrenal; HREC: Human Research Ethic Committee; IU: international units; MCI: mild cognitive impairment.

Caption for figure 1: Flow of participants through the study.

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578

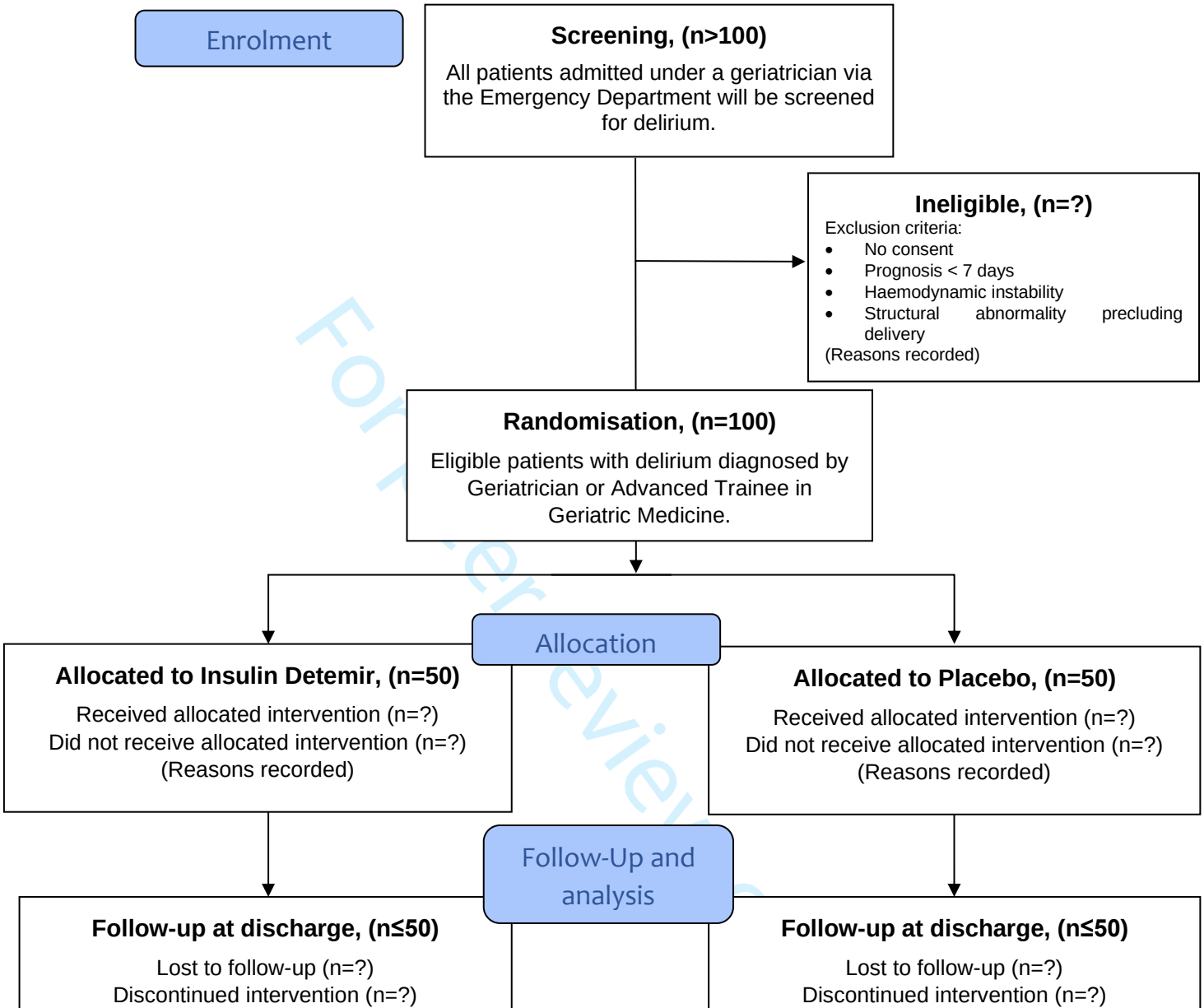
Table 1 – List of measures collected at baseline (B), daily during intervention (D), hospital discharge (DC), 6 months follow up (6M).

Information collected for all participants	B	D	DC	6M	O
Socio-demographics					
Age, gender, education, occupation, handedness, marital status.	x				
Place of residence and new admission to Residential Aged Care Facility.	x		x	x	S
Medical and functional status					
Medical history, medication use, history of delirium and dementia, precipitating factor(s) in delirium.	x				
Informant Questionnaire on Cognitive Decline in the Elderly (66).	x			x	
Barthel index (54), modified Instrumental Activities of Daily Living (55).	x			x	S
Charlson Comorbidity Index (67), Acute Physiology, Age, Chronic Health Evaluation III (68), Clinical Frailty Scale (69).	x				
Baseline blood tests, Apolipoprotein E4 status	x				
Delirium and neuropsychological					
Delirium motor-subtyping scale (40).	x				
Delirium presence and severity - Confusion assessment method (36), Delirium Index (39).	x	x		x	S
Mini-mental status examination (70).	x			x	
Geriatric Depression Scale (71).	x			x	
Wechsler Adult Intelligence Scale IV Digit Span test (72), Trail Marking Test A and B (73), Wechsler Memorial Scale III Mental Control (74), clock drawing task, word generation tasks and memory impairment screen (75).				x	S

Duration of delirium, patients discharged with residual delirium will be reviewed daily for up to one week post-discharge.		x			P
Inpatient Assessments and safety					
Percentage doses successfully administered.			x		
Use of antipsychotics – type, dose and frequency of administration will be recorded and converted to total equivalence dose of antipsychotic during admission and median daily dose.			x		S
Hospital complications, prespecified from Australian Commission on Safety and Quality in Health Care list.			x		S
Adverse events – assessed during clinical review.		x			
Blood glucose level will be measured four times daily using a finger prick measurement.	x	x			
Length of stay.			x		S
Mortality rate.			x	x	S

Note: x = measurement to be taken at prespecified time, O = outcome measure, P = primary, S = secondary

Figure 1. CONSORT study flow diagram.



Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

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

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1, 6
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	5, 6
Protocol version	#3	Date and version identifier	N/A
Funding	#4	Sources and types of financial, material, and other support	16
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 16

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	16
Roles and responsibilities: sponsor and funder	#5c	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	16
Roles and responsibilities: committees	#5d	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)	10, 11, 13
Introduction			
Background and rationale	#6a	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, 4, 8-10
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	8
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	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)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	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, 6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	6, 7

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8, 9
Interventions: modifications	#11b	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 -11
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	11
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	#12	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	11, 12
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	table 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6, 7
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	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	8

Allocation concealment mechanism	#16b	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	8
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6-8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10, 11
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate 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	table 1, 13
Data collection plan: retention	#18b	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	7, 12
Data management	#19	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	13
Statistics: outcomes	#20a	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	12
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12, 13

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12, 13
Methods: Monitoring			
Data monitoring: formal committee	#21a	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	11, 13
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10, 11
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10, 11
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10, 11
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	6, 16
Protocol amendments	#25	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)	6
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	7
Confidentiality	#27	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	13

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	table 1
Dissemination policy: trial results	#31a	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	14
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	14
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	14
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	13
Biological specimens	#33	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	8

Notes:

- 18a: table 1, 13 The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons Attribution License CC-BY-NC. This checklist was completed on 28. February 2021 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Intranasal insulin for treatment of delirium in older hospitalised patients: study protocol for a randomised controlled trial

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Title: Intranasal insulin for treatment of delirium in older hospitalised patients: study protocol for a randomised controlled trial

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Word count: Abstract = 247 words. Body = 3804

Key words: delirium, treatment, intranasal insulin, older, drug therapy.

Abstract

Introduction: Delirium is one of the most common conditions diagnosed in hospitalised older people and is associated with numerous adverse outcomes, yet there are no proven pharmacological treatments. Recent research has identified cerebral glucose hypometabolism as a pathophysiological mechanism offering a therapeutic target in delirium. Insulin, delivered via the intranasal route, acts directly on the central nervous system and has been shown to enhance cerebral metabolism and improve cognition in patients with mild cognitive impairment and dementia. This trial will determine whether intranasal insulin can reduce the duration of delirium in older hospitalised patients.

Methods and analysis: This is a prospective randomised, placebo-controlled, double blind study with 6 months follow up. One hundred patients aged 65 years or older presenting to hospital with delirium admitted under Geriatric Medicine will be recruited. Participants will be randomised to intranasal insulin detemir or placebo administered twice daily until delirium resolves, defined as Confusion Assessment Method (CAM) negative for two days, or discharge from hospital. The primary outcome measure will be duration of delirium using the CAM. Secondary outcome measures will include length of hospital stay, severity of delirium, adherence to treatment, hospital complications, new admission to nursing home, mortality, use of antipsychotic medications during hospital stay and cognitive and physical function at 6-months post-discharge.

Ethics and dissemination: This trial has been approved by the South Eastern Sydney Human Research and Ethics Committee. Dissemination plans include submission to a peer-reviewed journal for publication and presentation at scientific conferences.

Trial registration: ACTRN12618000318280

Strengths and Limitations:

- The study design is pragmatic, inclusive and representative of real-world older hospitalised patients who are often omitted from research due to multimorbidity.
- The primary outcome, duration of delirium, is clinically relevant with longer duration of delirium predicting worse outcomes in patients.
- This is a single site trial based in Sydney, Australia therefore generalisability may be restricted.
- Bedside assessment of delirium will occur daily rather than multiple times per day, meaning diurnal fluctuations in behaviour will be captured by record review and informant history.
- Patients in this study will be reviewed in person by trained assessors daily for up to one-week post-discharge, however, assessment after one week is beyond the resources allocated for this trial.

Background

Delirium is common, with figures reporting 10-35% of older people are delirious on admission to hospital (prevalent delirium) and up to another 29% will become delirious during their admission (incident delirium) (1). It is characterised by sudden and fluctuating disturbances in cognition, attention and awareness (2). The sequelae of delirium are manifold and extend beyond the acute hospitalisation; increased mortality, new cognitive impairment, accelerated dementia, loss of independence and increased admission to nursing home(3, 4). In older patients, delirium is independently associated with a two-fold increase in mortality at 12 months (5). Longer duration and increased severity of delirium predict poorer outcomes in older patients (6).

Studies suggest that only 30% of incident delirium is potentially preventable with non-pharmacological multimodal intervention (7). Current management focuses on identifying and treating the underlying cause of delirium combined with non-pharmacological interventions to provide an optimal

environment for brain recovery and reduce the risk of potentially avoidable complications such as falls and pressure injuries.

Pharmacological management is focused on symptomatic control with antipsychotics. However, evidence does not support the use of antipsychotics for delirium and a recent randomised controlled trial demonstrated worsening symptoms and increased mortality (8, 9). At this point in time there are no proven pharmacological interventions to prevent or manage delirium.

Delirium pathophysiology is poorly understood, although several hypotheses exist (10). These include neuroinflammation (11), neurotransmitter dysregulation (12), neuroendocrine dysregulation (13) and neural network dysconnectivity (14). As delirium is a complex and heterogeneous disorder, it is likely that several of these mechanisms may contribute to the development of delirium with varying effect depending on pre-existing patient vulnerabilities and the aetiology of the acute precipitant (15). However, regardless of the underlying cause, delirium presents in a recognisable and stereotyped manner (phenotypically hypoactive, hyperactive and mixed) and the hypothesis that a "final common pathway" may exist should not be disregarded.

Research has identified altered cerebral perfusion and metabolism as a feature of delirium. Delirious patients have higher cerebrospinal fluid (CSF) lactate and lower neuron-specific enolase suggesting suppressed aerobic metabolism during an episode of delirium (16, 17). Two studies have demonstrated cerebral glucose hypometabolism during delirium using fluorodeoxyglucose positron emission tomography (FDG-PET) (18, 19). Haggstrom et al have demonstrated a correlation between posterior cingulate cortex hypometabolism and attention as well as evidence of improved cortical glucose metabolism with resolution of delirium (18). Neuroimaging studies using a variety of modalities have demonstrated reduced cerebral perfusion, decreased cerebral oxygenation and abnormal cerebral autoregulation during an episode of delirium (20, 21). As cerebral blood flow and metabolism are closely coupled and considered to reflect synaptic activity(22), correction of perfusion and metabolism abnormalities may improve clinical outcomes in delirium.

It is now well established that the brain is an insulin sensitive organ; insulin receptors are widely expressed in the brain, with greatest saturation in the corticolimbic structures (23). Insulin enhances learning and memory by modulating neuronal growth, metabolism, plasticity and cholinergic function (23, 24).

The role of glucose metabolism in the pathogenesis of neurodegenerative disease is a growing area of research (25). Mild Cognitive Impairment (MCI) and Alzheimer's Dementia (AD) have been characterised as states of brain-specific insulin resistance and deficiency sometimes called "type 3 diabetes" (26). Patients with early stage AD demonstrate pronounced insulin and insulin-like growth factor deficiency and resistance which progress with severity of neurodegeneration (23). Administration of intravenous (IV) insulin while maintaining fasting serum glucose levels improves memory in patients with Alzheimer's Disease (27). However, therapeutic administration of IV insulin is not feasible or safe due to the substantial risk of systemic hypoglycaemia.

The intranasal route of delivery provides a non-invasive and safe means of transporting insulin to the brain. A recent systematic review identified seven studies (total, N =293) examining the effect of intranasal insulin on MCI or AD, of which six demonstrated significant improvements in verbal memory (28). Positive outcomes in functional status were also observed (29-31). Improvements in attention, visuospatial memory and executive function have also been demonstrated in other populations (32-34).

One pilot trial has assessed the effect of intranasal insulin on delirium prevention in a cohort of 21 older cardiothoracic surgical patients (35). The incidence of postoperative delirium was lower in the intranasal group (18% vs 40%) although the result was not statistically significant, likely due to the small sample size. No serious adverse events were reported (36).

Given that intranasal insulin improves cognition as well as cerebral perfusion and metabolism, this trial will investigate its potential role in treatment of delirium.

This randomised controlled trial will evaluate whether intranasal insulin, compared to placebo, can reduce the duration of delirium in older patients admitted under Geriatric Medicine.

Methods

Design

This is a single site, randomised, double-blind, placebo-controlled trial of 100 older people diagnosed with delirium on admission to hospital (prevalent delirium). Figure 1 gives an overview of study design.

This research will be conducted in accordance with the Declaration of Helsinki. As required by the New South Wales Guardianship act 1987 (part 5), New South Wales Civil and Administrative Tribunal, approval to conduct this clinical trial has been obtained (case number 2017/00204946). The trial was registered in the Australian and New Zealand Clinical Trial Registry on 5 March 2018 (ACTRN12618000318280).

Population

The study population will comprise older people admitted under a Geriatrician at a large tertiary hospital in metropolitan Sydney, Australia. Potential participants must be a) diagnosed with prevalent delirium, b) receiving inpatient care on the Geriatric Medicine Wards, c) age > 64 years, d) have a consenting "person responsible" and e) be enrolled in the trial within 48 hours of admission to hospital. People with known cognitive impairment and dementia will be included.

Exclusion criteria include a) people who are haemodynamically unstable (based on treating physicians judgement guided by activation of a "red zone response" on the NSW Health Standard Adult General Observation Chart(37)), b) have a predicted life expectancy of less than seven days as

judged by the admitting geriatrician, c) have an allergy to insulin detemir formulation or d) a structural abnormality precluding the use of the nasal drug delivery device, e) proven or suspected COVID-19. People will also be excluded if consent is not obtained or they were previously enrolled in the trial. Non-English-speaking patients who are unable to participate in cognitive assessments will also be excluded. The trial will not include patients with incident delirium.

Screening and Evaluation of delirium

Within the emergency department or on transfer to the Geriatric Medicine Ward, all patients age >64 years will be screened by nursing staff for delirium using the Confusion Assessment Method (CAM) (38, 39). Patients with delirium diagnosed by a Geriatrician or Advanced Trainee in Geriatric Medicine using the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition criteria (DSM 5) will be considered for the trial (40).

Study team members will use the CAM to conduct daily delirium assessments between 12-2pm. All members of the study team will undergo formal training using the CAM. Bedside assessment will be supplemented by review of the medical records and collateral history from the patient's carer or ward staff where appropriate. The presence of delirium will be documented using the long form CAM (38). Delirium severity will be assessed using the Delirium Index (DI) (41). Delirium clinical subtype will be assessed using the abbreviated version of the Delirium Motor Subtyping Scale (DMSS-4) (42). A Mini-Mental Status Examination (MMSE) will be used to complete the CAM and DI during the initial assessment and a standardised structured assessment will be conducted on subsequent days (see appendix A).

Interrater reliability using the CAM and DI will be assessed using Cohen's kappa coefficient based on twenty patient reviews (43).

Consent

Consent will involve conversations regarding the study risks, benefits and burdens between the researchers, patient and the "person responsible" (substitute decision maker according to the New South Wales Guardianship Act 1987). To avoid a delay in initiation of the intervention, where a person responsible is unable to attend the hospital to sign the consent, an initial verbal consent may be granted (by phone) and written consent obtained as soon as possible.

Consent to remain in the trial will be obtained from the patient if capacity returns. Should the patient decline further involvement in the trial the researcher will ask the patient for consent to use trial data up until the time of withdrawal in the final analysis.

Consent will also be obtained for the collection and study of patient blood specimens.

Assessment over the study period

Table 1 highlights the measures to be undertaken at each pre-determined time point. Measurements will be taken daily while receiving the intervention. Patient assessment will also occur at discharge from hospital and 6 months post discharge.

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184 **Table 1 – List of measures collected at baseline (B), daily during intervention (D), hospital discharge (DC), 6 months follow up (6M).**

Information collected for all participants	B	D	DC	6M	O
Socio-demographics					
Age, gender, education, occupation, handedness, marital status.	x				
Place of residence and new admission to Residential Aged Care Facility.	x		x	x	S
Medical and functional status					
Medical history, medication use, history of delirium and dementia, precipitating factor(s) in delirium.	x				
Informant Questionnaire on Cognitive Decline in the Elderly (44).	x			x	
Barthel index (45), modified Instrumental Activities of Daily Living (46).	x			x	S
Charlson Comorbidity Index (47), Acute Physiology, Age, Chronic Health Evaluation III (48), Clinical Frailty Scale (49).	x				
Baseline blood tests, Apolipoprotein E4 status	x				
Delirium and neuropsychological					
Delirium motor-subtyping scale (42).	x				
Delirium presence and severity - Confusion assessment method (38), Delirium Index (41).	x	x		x	S
Mini-mental status examination (50).	x			x	
Geriatric Depression Scale* (51).	x			x	

Wechsler Adult Intelligence Scale IV Digit Span test (52), Trail Making Test A and B (53), Wechsler Memorial Scale III Mental Control (54), clock drawing task, word generation tasks and memory impairment screen (55).				x	S
Duration of delirium, patients discharged with residual delirium will be reviewed daily for up to one week post-discharge.		x			P
Inpatient Assessments and safety					
Percentage doses successfully administered.			x		S
Use of antipsychotics – type, dose and frequency of administration will be recorded and converted to total equivalence dose of antipsychotic during admission and median daily dose.			x		S
Hospital complications, prespecified from Australian Commission on Safety and Quality in Health Care list.			x		S
Adverse events – assessed during clinical review.		x			
Blood glucose level will be measured four times daily using a finger prick measurement.	x	x			
Length of stay.			x		S
Mortality rate.			x	x	S

Note: x = measurement to be taken at prespecified time, O = outcome measure, P = primary, S = secondary

*If the patient is unable to engage during the initial assessment, repeat the test in subsequent days when the patient is able to engage.

Dementia status will be determined by a history of dementia diagnosis (informant history and medical record review) and/or an average IQCODE score >3.44 (44).

In addition to routine blood tests, 20millilitres of blood will be taken from each patient and stored for later analysis, including the effect of Apolipoprotein E4 (APOE4) status on study outcomes.(56) Specimens will be frozen and stored at -80 degrees Celsius in the University of New South Wales Lowy Biorepository.

Randomisation and blinding

Permutated block randomisation will be conducted with a block size of 4 and 25 blocks using a computer-generated algorithm. An independent clinical trials pharmacist will create the randomisation schedule which will be provided to the clinical trials pharmacy staff responsible for production and dispensing of the medication. Each vial of insulin or placebo will be labelled with a sequentially allocated randomisation number, which will become that patient's study number.

Participants, research and ward staff will be blinded to treatment allocation.

Intervention

Patients will receive 20 international units (IU) of long-acting insulin (detemir) or a placebo of normal saline intranasally twice daily at 8am and 8pm via a commercially available drug delivery device (ViaNase delivery device, Kurve Technology, Bothell, Washington). This device has been used successfully in previous trials of intranasal insulin in cognitive impairment (30, 31). The device will release 20IU insulin detemir or placebo intranasally via a small nose piece over a 40 second period. Patients will receive 20 seconds per nostril twice daily and during administration be instructed to breath normally through the nose.

Following intranasal administration, insulin enters the brain either through direct entry via the cribriform plate and the olfactory nerves or via specific receptors in the blood-brain barrier or a combination of the two (57). In 15-30 minutes, insulin peptides are detected within the cerebral cortex and hippocampus (58). Compared to the subcutaneous route, intranasal administration of insulin demonstrates an approximately 2000-fold increase in the $AUC_{brain:plasma}$ ratio, meaning at similar doses the intranasal route reaches comparable or increased brain insulin concentration but substantially lower plasma concentration (59).

The total daily dose of 40IU of insulin detemir is based on research by Claxton et. al demonstrating safety and efficacy in older patients with Alzheimer's dementia. In this trial, 60 patients with mild cognitive impairment or mild-to-moderate AD received either placebo, 20IU of insulin detemir, or 40IU of insulin detemir intranasally for 21 days. Participants receiving 40IU of insulin detemir demonstrated significant improvements in verbal and visuospatial working memory. No statistically significant effect was found in the 20IU detemir group. No treatment-related severe adverse events were reported (56).

Pre-prepared, spare vials and in-use devices will be stored between 2-8 degrees Celsius in the ward medication fridge.

The medication will be administered by ward registered nurses specifically trained for the trial. Nurses will record challenges regarding administration of the intervention, including partially received or omitted doses, in the electronic patient record which will be reviewed by trial staff daily.

The intervention will cease following two consecutive CAM negative days; this criteria has been successfully adopted in other studies assessing delirium duration.(60) The intervention will be discontinued for patients with subsyndromal delirium (defined by the presence of one or more CAM symptoms without meeting the criteria for delirium) (61).

Cessation of treatment with the study intervention will also occur if:

- The patient is discharged from the hospital

- Patient or treating clinician requests discontinuation
- Unacceptable side effects from study medications (defined by National Cancer Institute Common Criteria for Adverse Events; Common Terminology Criteria for Adverse Events version 4.0)
- Participants who in the opinion of the investigator are not well enough to continue in the study
- Adverse events related to the study medicine are unacceptable to the participant/carer or clinician in charge e.g. symptomatic or severe hypoglycaemia (blood sugar level <3.0mmol/L)
- Treatment is deemed ineffective, defined as no improvement in delirium index over 7 days.

Patients withdrawn from the study will be included in statistical analysis on an intention-to-treat basis.

If delirium recurs after resolution of the initial episode (i.e. hospital acquired delirium) the intervention will not be recommenced.

Safety

Studies have demonstrated that less than 3% of intranasally-delivered insulin is detectable in the serum and as a result intranasal insulin has a negligible risk of hypoglycaemia (28, 62). A systematic review on the safety of intranasal insulin included 38 studies (N=1092) and found no cases of hypoglycaemia or severe adverse events (63). The most commonly reported side effects were transient and local to the nasal area including nasal tingling and burning, less commonly rhinitis and nasal bleeding occurred.

Although the risk of hypoglycaemia is largely theoretical, blood glucose levels will be measured at baseline and four times daily during the study intervention (07:00, 13:00, 19:00, 22:00). As adequate

and uninterrupted sleep is a core principle in delirium management and disturbed sleep can precipitate or exacerbate delirium, blood glucose levels will not be taken overnight.

Adverse events will be assessed daily through participant interview supplemented by review of the electronic medical record. Serious adverse events as defined by the International Conference on Harmonisation Guidelines for Good Clinical Practice will be reported in accordance with local ethics requirements. An independent data and safety monitoring board (DSMB) will oversee the study and meet after each twenty patients. Serious adverse events will be discussed with the lead investigator immediately and reported to the Human Research Ethics Committee (HREC) and trial DSMB within 24 hours.

Delirium is associated with a high in-hospital mortality rate, previously demonstrated to reach 35% in an older population (64). As such, a key role of DSMB will be to review all deaths and serious adverse events in detail to determine if the adverse event was in keeping with the natural history of the illness or could be attributed to the study intervention (65). Should concerns arise regarding patient safety the DSMB may request to unblind for decision making purposes.

There are two main scenarios which could prompt DSMB to request termination of the study. Firstly, if there are a significant number of serious adverse events possibly attributed to the intervention leading to patient safety concerns and secondly, significant benefit from the intervention. Should termination of the trial be requested, researchers would be unblinded and data analysis would occur. The HREC and participants would be informed the trial was stopped and reasons for termination given.

Outcomes

The primary and secondary outcomes are outlined in table 1. The primary outcome will be duration of delirium in days. Delirium assessment will be conducted daily from enrolment until delirium

resolution, defined as two consecutive days (48hours) CAM negative. Patients discharged with delirium will be followed up in person daily for up to one week to assess for delirium resolution. Secondary outcomes will determine if intranasal insulin compared to placebo decreases acute length of hospital stay, reduces severity of delirium, reduces hospital complications, reduces new admission to nursing home, decreases mortality and decreases use of antipsychotic medications during an inpatient stay. Patients will be followed up at 6 months post-discharge to assess if intranasal insulin reduces mortality and preserves cognition and function. Adherence to the intervention will be measured by percentage of doses successfully administered.

Sample size

Power analysis (with 5% significance and 80% power) was performed using published data which shows the mean duration of delirium clustered at approximately 8 days in Geriatric medicine ward populations(66, 67). Power calculation shows reducing delirium duration by two days (from 8 days to 6 days) requires 36 in each arm for a total of 72 patients. Allowing for a 30% dropout rate, a total of 100 participants will be sought.

Statistical Analysis

Statistical analysis will be conducted using IBM SPSS Statistics software. An intention-to-treat approach will be adopted for all analyses and statistical significance assumed at the level of 5% ($P<0.05$). Baseline characteristics will be reported for the overall population and separately for each group.

The primary outcome, duration of delirium measured in days, will be analysed first with a Mann Whitney U test which has high statistical power (68) and then using survival analysis Cox

proportional hazard method including dementia, nursing home status, severity of acute illness (APACHE III) and comorbidity as covariates. Sensitivity analysis will be conducted using normality-improving data transformations or Gamma regression with a log link according to the distribution of the primary outcome. Analysis will include in hospital death as a competing risk. For the major secondary outcome, trajectory of delirium severity measured by the delirium index over time, a generalised linear mixed model will be used. Binary outcomes like mortality (in-hospital and at six months) and institutionalisation will be evaluated using a modified Poisson regression (69). A linear regression will assess possible preservation of function, measured by Barthel index (45) and modified Instrumental Activities of Daily Living (46), and for all other linear secondary outcomes. Bootstrapping will be applied if the models fail to satisfy the normality assumptions. For length of hospital stay, a log-linear or gamma regression with a log link will be implemented. The number of hospital complications and the use of antipsychotics during hospitalization will be reported.

Subgroup analysis stratifying by age, sex, dementia and APOE status will be conducted.

Data Management

Data will be collected by trained researchers and stored on a password protected database. One researcher will be responsible for data entry while another member of the study team will monitor the accuracy of data by cross-checking a random 10% sample of subjects.

Paper files of individual records will be stored in a locked cabinet in a secure location accessible to authorised members of the study team only. Electronic data will be entered in a de-identified format and stored on a password-protected secure server. The complete data set will be stored on the University of New South Wales Data Archive and will be made available at the completion of the trial on reasonable request.

Patient and public involvement

A public representative approved trial concept, design and consent procedures as part of the application to New South Wales Civil and Administrative Tribunal.

Ethics and dissemination:

The trial methods, protocol and consent procedures were approved by the South Eastern Sydney Human Research and Ethics Committee (HREC 16_320). Results of the trial will be published in biomedical journals and presented at international scientific conferences. Social media platforms will be used to inform the general public about the results. Authorship on publications related to this study will follow standard eligibility guidelines ensuring significant contribution.

Discussion

Delirium is a debilitating condition commonly affecting older people in hospital and for which there are no registered treatments. It has been consistently demonstrated that longer duration of delirium predicts worse outcomes, including higher mortality and new admission to residential aged care facility (6, 70). Although the pathophysiological mechanisms are incompletely understood, it is probable that an episode of delirium causes irreversible neuronal damage leading to sustained cognitive and functional impairment (71), with prolonged delirium exposure leading to greater cerebral damage.

To date, there are no trials assessing intranasal insulin as a treatment for delirium, however, it could improve cognitive and clinical outcomes for delirious patients via a variety of mechanisms. Intranasal insulin increases cerebral perfusion (33, 72-74) and increases or maintains cerebral glucose metabolism on FDG-PET (75, 76). In young healthy adults and patients with type II diabetes mellitus,

intranasal insulin enhances functional connectivity within the default mode network, an important centre for higher cognitive processes in which delirious patients demonstrate dysconnectivity (14, 77, 78). The hypothalamic-pituitary-adrenal (HPA) axis is also insulin responsive and following administration of intranasal insulin healthy populations demonstrate diminished saliva and plasma cortisol (32, 79). As aberrant HPA axis activity is hypothesised to contribute to delirium pathophysiology, modification of this pathway may also lead to improved outcomes (13).

We anticipate this trial will be pragmatic, inclusive and representative of real-world Geriatric medicine inpatients. As such, we will include patients with pre-existing dementia and those residing in residential aged care facilities. This vulnerable population is at highest risk for delirium yet commonly under-represented in therapeutic trials.

An important aspect of this study will be patient tolerability of an inhaled nasal solution twice daily. Ward registered nurses administering intranasal insulin will receive training in both administration and subsequent documentation of the intervention. We will report on adherence and patients will be analysed on an intention-to-treat basis.

As duration of delirium is perhaps the most clinically relevant outcome for both clinicians and patients, we have chosen this as the primary outcome for the trial. The mean duration of delirium in Geriatric medicine inpatients has been demonstrated to be 8 +/- 9 days, however, symptoms of delirium can persist for up to 12 months (66). We anticipate some patients, particularly those returning to high level care residential aged care facilities, will be discharged with delirium and this group will be followed up daily for up to one week to assess for delirium resolution. Daily assessment after one week is beyond the allocated resources for this trial.

If found to be efficacious, this would lead to multicentre trials to confirm these findings. There would also be the opportunity to explore intranasal insulin in prevention of delirium and its role across settings, including in the intensive care and post-operative populations which also represent vulnerable patient groups.

Should the intervention reduce the duration of delirium the benefits to patients and their families could be significant, both in alleviating acute distress and longer-term negative sequelae of delirium. The treatment also has the potential to save significant financial resources related to both the acute treatment of delirium and the residual effects with regards to loss of independence and higher care needs after resolution of delirium. Finally, irrespective of the outcome, this trial will contribute to our understanding of the pathophysiological mechanisms of delirium particularly the role of impaired cerebral perfusion and metabolism.

Declarations

Ethics approval and consent to participate: The trial methods, protocol and consent procedures were approved by the South Eastern Sydney Human Research and Ethics Committee (HREC 16_320). As required by the New South Wales Guardianship act 1987 (part 5), New South Wales Civil and Administrative Tribunal, approval to conduct this clinical trial has also been obtained (case number 2017/00204946).

Consent for publication: Not applicable.

Availability of data and materials: Materials including data collection and consent forms can be accessed by contacting the corresponding author.

Competing interest: The authors declare that they have no competing interests.

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Author contributions: GC initiated the study and is the trial sponsor. AN, AM and GC designed the original protocol. JC and MA provided substantial input in study processes and logistics. BTu

provided expertise in the area of Endocrinology. BTo provided extensive guidance on the statistical analysis. All authors contributed to the writing of the manuscript and approved the final version.

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Abbreviations: AD: Alzheimer's dementia; AUC: area under the curve; APOE: Apolipoprotein E; CAM: confusion assessment method; CSF: cerebrospinal fluid; DI: delirium index; DSM: Diagnostic and Statistical Manual of Mental Disorders; DSMB: data and safety monitoring board; FDG-PET: fluorodeoxyglucose positron emission tomography; HPA: hypothalamic-pituitary-adrenal; HREC: Human Research Ethic Committee; IU: international units; MCI: mild cognitive impairment.

Caption for figure 1: Flow of participants through the study.

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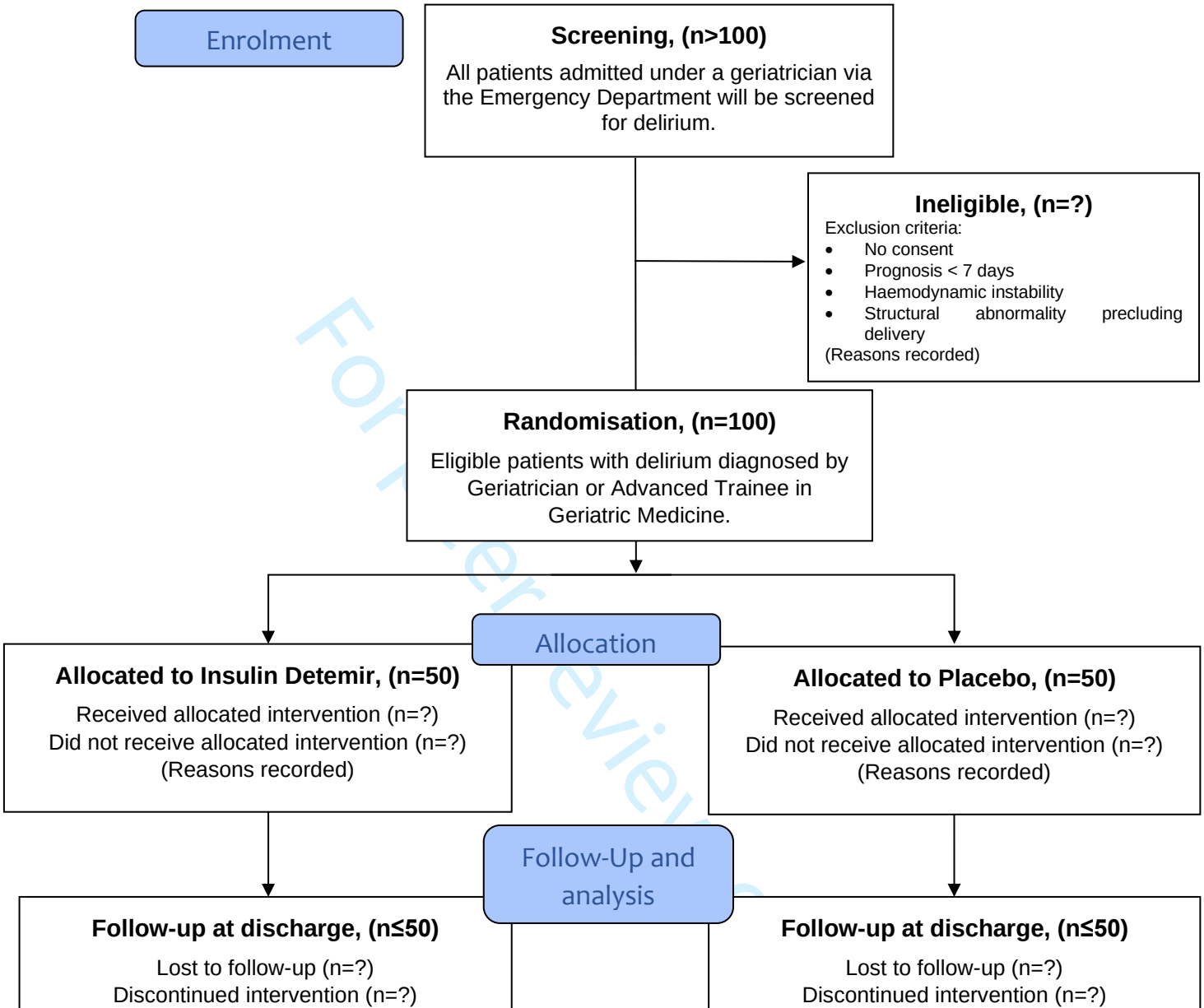
Figure 1. CONSORT study flow diagram.



Daily Structured Assessment (not initial)
Electronic Medical Record Review Administration of intervention: - Review if administered successfully, review nursing notes regarding administration, tolerability and side effects. Review glycaemic control. Review nursing and medical notes*: - Evidence of fluctuating levels of consciousness and behaviour, disturbed sleep cycle, perceptual changes including hallucinations. - Evidence of hospital acquired complications. - New prescription of antipsychotics or benzodiazepines.
Informant history from patient's family and health care workers where available.
Patient review General observations*: - Alertness, level of consciousness, motor activity, hallucinations. Trial related questions: - Does the patient recall receiving the intervention? Side effects? Nasal irritation? Trial related issues? Orientation and thought content: - Assess orientation* to: date of birth, current year, place, age, day of week, month. - Is the patient aware of the reason for hospitalisation? Duration of hospital admission? - If required consider specific questions to assess disorganised thinking# (Does a stone float on water? Are there fish in the sea? Do you hit a nail with a hammer?) Registration*: - Three-word registration (rotating words daily to avoid learning bias) Attention: - Ability to participate in conversation and shift attention. - Five letter word backwards* (rotating single syllable words daily to avoid learning bias) - Months of the year backwards (<7 months) - Supplementary tests as required#^: SAVEAHAART (≥2 errors), days of the week backwards (≥1 errors), five-digit span forwards(≥1 errors), three-digit span backwards(≥1 errors). Recall* Assessment of perceptual abnormalities: - Have you seen and experienced anything unusual or unexpected*? - Other questions: Do you feel safe? Do you think anyone is out to harm you? Are you being well looked after in the hospital?
Complete short and long from confusion assessment method and delirium index. - If the patient is negative on the short form confusion assessment for two consecutive days cease the trial.

*Required for delirium index/long-form confusion assessment method

#Consider for patients with delirium superimposed on dementia

^Consider if lower education, learning bias suspected

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, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	6,7
Protocol version	#3	Date and version identifier	N/A
Funding	#4	Sources and types of financial, material, and other support	17
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 17
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	17
Roles and responsibilities: sponsor and funder	#5c	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	17
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	11, 12, 14

		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	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, 9-10
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	9
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	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)	6
Methods: Participants, interventions, and outcomes			
Study setting	#9	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	6,7

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6, 7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9,10
Interventions: modifications	#11b	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)	10-12
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	11-12
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	#12	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	12

Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	table 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	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	8
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	8,9

		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6-9
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	11,12
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate 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	table 1, 14

Data collection plan: retention	#18b	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	8, 13
Data management	#19	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	13
Statistics: outcomes	#20a	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	13
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and	11, 13

		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	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10- 12
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10-12
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	14
Protocol amendments	#25	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)	6

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7-8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	7-8
Confidentiality	#27	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	14
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	16-17
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	table 1
Dissemination policy: trial results	#31a	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	14

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	14
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	14
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	attached
Biological specimens	#33	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	8

Notes:

- 18a: table 1, 13 The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons Attribution License CC-BY-NC. This checklist was completed on 28. February 2021 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai