

BMJ Open 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 2 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 postdischarge.

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 number ACTRN12618000318280.

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

Strengths and limitations of this study

- 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 1-week postdischarge, however, assessment after 1 week is beyond the resources allocated for this trial.

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 twofold 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



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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 for use on general hospital wards.

Delirium pathophysiology is poorly understood, although several hypotheses exist.¹⁰ These include neuroinflammation,¹¹ neurotransmitter dysregulation,¹² neuroendocrine dysregulation¹³ 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 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 insulin while maintaining fasting serum glucose levels improves memory in patients with Alzheimer's disease.²⁷ However, therapeutic administration of intravenous 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 randomised placebo controlled trial has assessed the effect of intranasal insulin on delirium prevention in a cohort of 80 older patients undergoing laparoscopic gastrointestinal tumour resection.³⁵ The incidence of postoperative delirium within five days of surgery was lower in the intranasal group (12.5% vs 47.5%, P=0.001). There were no differences in blood glucose levels or adverse events between groups.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 with 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).

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 New South Wales Health Standard Adult General Observation Chart³⁶), (B) have a predicted life expectancy of less than 7 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 and (E) proven or suspected

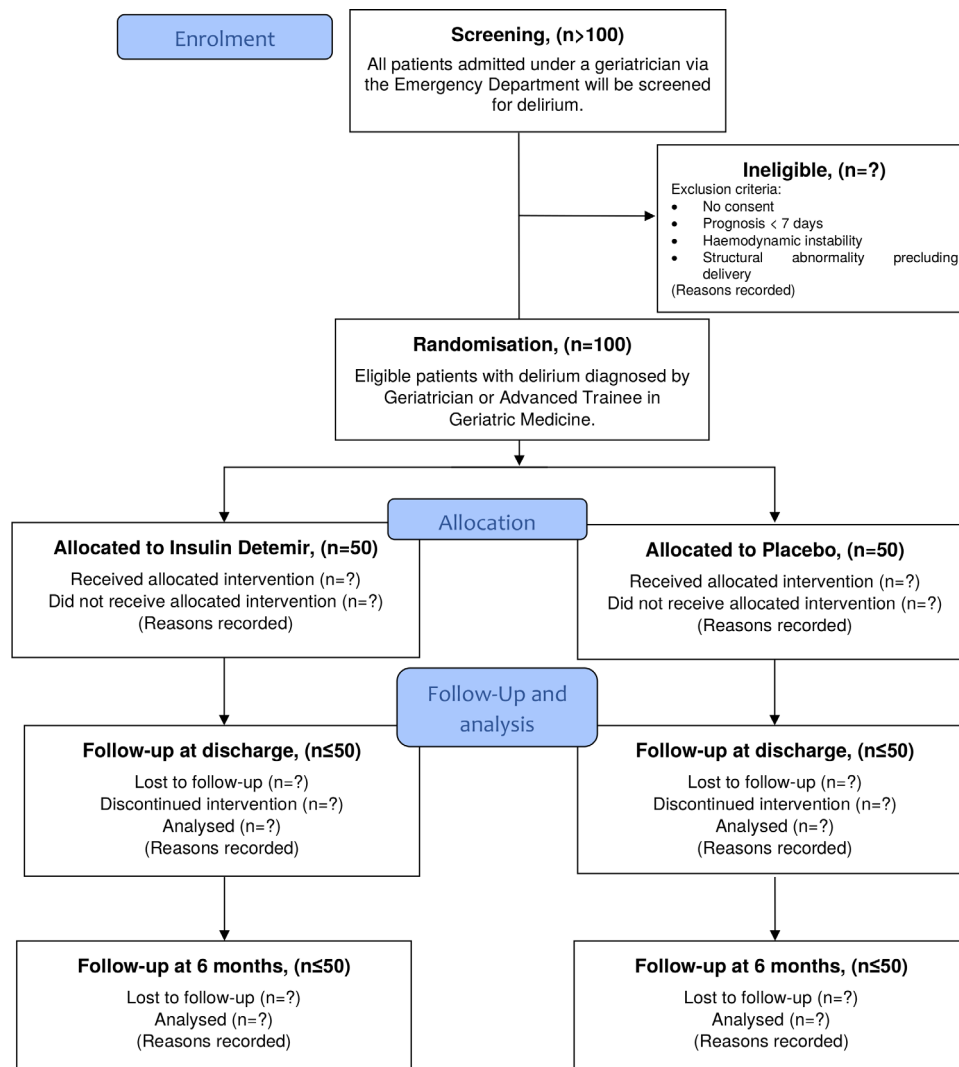


Figure 1 Flow of participants through the study.

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).^{37 38} 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 will be considered for the trial.³⁹

Study team members will use the CAM to conduct daily delirium assessments between 12:00 and 15:00 hours. 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.³⁷ Delirium severity will be assessed using the Delirium Index (DI).⁴⁰ Delirium clinical subtype will be assessed using the abbreviated version of the Delirium Motor Subtyping Scale.⁴¹ A Mini-Mental Status Examination 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 online supplemental appendix A).

Inter-rater reliability using the CAM and DI will be assessed using Cohen's kappa coefficient based on twenty patient reviews.⁴²

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.

**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
Sociodemographics					
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 ⁴³	x			x	
Barthel Index, ⁵⁸ modified Instrumental Activities of Daily Living ⁵⁹	x			x	S
Charlson Comorbidity Index, ⁷⁰ Acute Physiology, Age, Chronic Health Evaluation III, ⁷¹ Clinical Frailty Scale ⁷²	x				
Baseline blood tests, apolipoprotein E4 status	x				
Delirium and neuropsychological					
Delirium motor-subtyping scale ⁴¹	x				
Delirium Presence and Severity-Confusion Assessment Method, ³⁷ Delirium Index ⁴⁰	x	x		x	S
Mini-Mental Status Examination ⁷³	x			x	
Geriatric Depression Scale* ⁷⁴	x			x	
Wechsler Adult Intelligence Scale IV Digit Span test, ⁷⁵ Trail Making Test A and B, ⁷⁶ Wechsler Memorial Scale III Mental Control, ⁷⁷ clock drawing task, word generation tasks and memory impairment screen ⁷⁸				x	S
Duration of delirium, patients discharged with residual delirium will be reviewed daily for up to 1-week postdischarge		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.

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 predetermined time point. Measurements will be taken daily while receiving the intervention. Patient assessment will also occur at discharge from hospital and 6 months postdischarge.

Dementia status will be determined by a history of dementia diagnosis (informant history and medical record review) and/or an average Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) score >3.44.⁴³

In addition to routine blood tests, 20 mL of blood will be taken from each patient and stored for later analysis, including the effect of apolipoprotein E4 (APOE4) status on study outcomes.⁴⁴ Specimens will be frozen and stored at -80°C 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 8:00 and 20:00 hours via a commercially available drug delivery device (ViaNase delivery device, Kurve Technology, Bothell, Washington, USA). 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 40s period. Patients will receive 20s 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.⁴⁵ In 15–30 min, insulin peptides are detected within the cerebral cortex and hippocampus.⁴⁶ Compared with the subcutaneous route, intranasal administration of insulin in mice demonstrates an approximately 2000-fold increase in the Area Under the Curve_{brain:plasma} ratio, meaning at similar doses the intranasal route reaches comparable or increased brain insulin concentration but substantially lower plasma concentration.⁴⁷

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 AD. 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.⁴⁴

Preprepared, spare vials and in-use devices will be stored between 2°C and 8°C 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.⁴⁸ 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).⁴⁹

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 V.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, for example, symptomatic or severe hypoglycaemia (blood sugar level <3.0 mmol/L).
- ▶ Treatment is deemed ineffective, defined as no improvement in DI 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 (ie, 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 50} A systematic review on the safety of intranasal insulin included 38 studies (N=1092) and found no cases of hypoglycaemia or severe adverse events.⁵¹ 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 and 22:00 hours). 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.⁵² 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.⁵³ 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. First, if there are a significant number of serious adverse events possibly attributed to the intervention leading to patient safety concerns and second, 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 (48 hours) CAM negative. Patients discharged with delirium will be followed up in person daily for up to 1 week to assess for delirium resolution. Secondary outcomes will determine if intranasal insulin compared with 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 postdischarge 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.^{54 55} Power calculation shows reducing delirium duration by 2 days (from 8 days to 6 days) requires 36 in each arm for a total of 72 patients. Allowing for a 30% drop-out rate, a total of 100 participants will be sought.

Statistical analysis

Statistical analysis will be conducted using IBM SPSS Statistics 26 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 power⁵⁶ and then using survival analysis Cox proportional hazard method including dementia, nursing home status, severity of acute illness (Acute Physiology, Age, Chronic Health Evaluation III (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 DI over time, a generalised linear mixed model will be used. Binary outcomes like mortality (in-hospital and at 6 months) and institutionalisation will be evaluated using a modified Poisson regression.⁵⁷ A linear regression will assess possible preservation of function, measured by Barthel Index⁵⁸ and modified Instrumental Activities of Daily Living,⁵⁹ 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 hospitalisation 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 deidentified 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 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 60} 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,⁶¹ 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 62–64} and increases or maintains cerebral glucose metabolism on FDG-PET.^{65 66} In young healthy adults and patients with type 2 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 67 68} 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 69} 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.⁵⁴ 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 1 week to assess for delirium resolution. Daily assessment after 1 week is beyond the allocated resources for this trial.

If found to be efficacious, this would lead to multi-centre trials to confirm these findings. There would also be the opportunity to further explore intranasal insulin in prevention of delirium and its role across settings, including in the intensive care and postoperative 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 regard 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.

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Contributors 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. BTu 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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