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

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2 randomised controlled trial

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21
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23
24 **Key words:** delirium, treatment, intranasal insulin, older, drug therapy.

25

26 Abstract

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

34 **Methods and analysis:** This is a prospective randomised, placebo-controlled, double blind study with
35 6 months follow up. One hundred patients aged 65 years or older presenting to hospital with delirium
36 admitted under Geriatric Medicine will be recruited. Participants will be randomised to intranasal
37 insulin detemir or placebo administered twice daily until delirium resolves, defined as Confusion
38 Assessment Method (CAM) negative for two days, or discharge from hospital. The primary outcome
39 measure will be duration of delirium using the CAM. Secondary outcome measures will include length
40 of hospital stay, severity of delirium, adherence to treatment, hospital complications, new admission
41 to nursing home, mortality, use of antipsychotic medications during hospital stay and cognitive and
42 physical function at 6-months post-discharge.

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

46 **Trial registration:** ACTRN12618000318280

47 Strengths and Limitations:

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2
3 49 • The study design is pragmatic, inclusive and representative of real-world older hospitalised
4
5 50 patients who are often omitted from research due to multimorbidity.
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8 51 • The results will add valuable insights into the neural mechanisms leading to delirium.
9
10 52 • Patients in this study will be followed up trained assessors daily for up to one-week post-
11
12 53 discharge, however, assessment after one week is beyond the allocated resources for this
13
14 54 trial.

55 Background

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

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

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

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2
3 73 Delirium pathophysiology is poorly understood, although several hypotheses exist. These include
4
5 74 neuroinflammation (10), neurotransmitter dysregulation (11), neuroendocrine dysregulation (12) and
6
7 75 neural network dysconnectivity (13). As delirium is a complex and heterogeneous disorder, it is likely
8
9
10 76 that several of these mechanisms may contribute to the development of delirium with varying effect
11
12 77 depending on pre-existing patient vulnerabilities and the aetiology of the acute precipitant (14).
13
14 78 However, regardless of the underlying cause, delirium presents in a recognisable and stereotyped
15
16 79 manner (phenotypically hypoactive, hyperactive and mixed) and the hypothesis that a “final common
17
18 80 pathway” may exist should not be disregarded.

21
22 81 Research has identified altered cerebral perfusion and metabolism as a feature of delirium. Delirious
23
24 82 patients have higher cerebrospinal fluid (CSF) lactate and lower neuron-specific enolase suggesting
25
26 83 suppressed aerobic metabolism during an episode of delirium (15, 16). Two studies have
27
28 84 demonstrated cerebral glucose hypometabolism during delirium using fluorodeoxyglucose positron
29
30 85 emission tomography (FDG-PET) (17, 18). Haggstrom et al have demonstrated a correlation between
31
32 86 posterior cingulate cortex hypometabolism and attention as well as evidence of improved cortical
33
34 87 glucose metabolism with resolution of delirium (17). Neuroimaging studies using a variety of
35
36 88 modalities have demonstrated reduced cerebral perfusion, decreased cerebral oxygenation and
37
38 89 abnormal cerebral autoregulation during an episode of delirium (19, 20). As cerebral blood flow and
39
40 90 metabolism are closely coupled and considered to reflect synaptic activity(21), correction of perfusion
41
42 91 and metabolism abnormalities may improve clinical outcomes in delirium.

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47 92 It is now well established that the brain is an insulin sensitive organ; insulin receptors are widely
48
49 93 expressed in the brain, with greatest saturation in the corticolimbic structures (22). Insulin enhances
50
51 94 learning and memory by modulating neuronal growth, metabolism, plasticity and cholinergic function
52
53 95 (22, 23).

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56 96 The role of glucose metabolism in the pathogenesis of neurodegenerative disease is a growing area of
57
58 97 research (24). Mild Cognitive Impairment (MCI) and Alzheimer’s Dementia (AD) have been
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3 98 characterised as states of brain-specific insulin resistance and deficiency sometimes called “type 3
4
5 99 diabetes” (25). Patients with early stage AD demonstrate pronounced insulin and insulin-like growth
6
7
8 100 factor deficiency and resistance which progress with severity of neurodegeneration (22).
9
10 101 Administration of intravenous (IV) insulin while maintaining fasting serum glucose levels improves
11
12 102 memory in patients with Alzheimer’s Disease (26). However, therapeutic administration of IV insulin
13
14 103 is not feasible or safe due to the substantial risk of systemic hypoglycaemia.

15
16
17 104 The intranasal route of delivery provides a non-invasive and safe means of transporting insulin to the
18
19 105 brain. A recent systematic review identified seven studies (total, N =293) examining the effect of
20
21 106 intranasal insulin on MCI or AD, of which six demonstrated significant improvements in verbal memory
22
23 107 (27). Positive outcomes in functional status were also observed (28-30). Improvements in attention,
24
25 108 visuospatial memory and executive function have also been demonstrated in other populations (31-
26
27 109 33).

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31 110 One pilot trial has assessed the effect of intranasal insulin on delirium prevention in a cohort of 21
32
33 111 older cardiothoracic surgical patients (34). The incidence of postoperative delirium was lower in the
34
35 112 intranasal group (18% vs 40%) although the result was not statistically significant, likely due to the
36
37 113 small sample size. No serious adverse events were reported (35).

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41 114 Given that intranasal insulin improves cognition as well as cerebral perfusion and metabolism, this
42
43 115 trial will investigate its potential role in treatment of delirium.

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46 116 This randomised controlled trial will evaluate whether intranasal insulin, compared to placebo, can
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48 117 reduce the duration of delirium in older patients admitted under Geriatric Medicine.
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118 **Methods**

119 **Design**

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

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

130 **Population**

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

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

1
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3 140 enrolled in the trial. Non-English-speaking patients who are unable to participate in cognitive
4
5 141 assessments will also be excluded. The trial will not include patients with incident delirium.
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10 11 12 143 Screening and Evaluation of delirium

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15 144 Within the emergency department or on transfer to the Geriatric Medicine Ward, all patients age
16
17 145 >64 years will be screened by nursing staff for delirium using the Confusion Assessment Method
18
19 146 (CAM) (36, 37). Patients with delirium diagnosed by a Geriatrician or Advanced Trainee in Geriatric
20
21 147 Medicine using the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition criteria (DSM
22
23 148 V) will be considered for the trial (38).

24
25
26
27 149 Study team members will use the CAM to conduct daily delirium assessments between 12-2pm. All
28
29 150 members of the study team will undergo formal training using the CAM. Bedside assessment will be
30
31 151 supplemented by review of the medical records and collateral history from the patient's carer or
32
33 152 ward staff where appropriate. The presence of delirium will be documented using the long form
34
35 153 CAM (36). Delirium severity will be assessed using the Delirium Index (DI) (39). Delirium clinical
36
37 154 subtype will be assessed using the abbreviated version of the Delirium Motor Subtyping Scale
38
39 155 (DMSS-4) (40).

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43 156 Interrater reliability using the CAM and DI will be assessed using Cohen's kappa coefficient based on
44
45 157 twenty patient reviews (41).
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49 158

50 51 52 159 Consent

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55 160 Consent will involve conversations regarding the study risks, benefits and burdens between the
56
57 161 researchers, patient and the "person responsible" (substitute decision maker according to the New
58
59
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3 162 South Wales Guardianship Act 1987). To avoid a delay in initiation of the intervention, where a
4
5 163 person responsible is unable to attend the hospital to sign the consent, an initial verbal consent may
6
7 164 be granted (by phone) and written consent obtained as soon as possible.
8
9

10 165 Consent to remain in the trial will be obtained from the patient if capacity returns. Should the
11
12 166 patient decline further involvement in the trial the researcher will ask the patient for consent to use
13
14 167 trial data up until the time of withdrawal in the final analysis.
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17 168 Consent will also be obtained for the collection and study of patient blood specimens.
18
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22 23 24 170 **Assessment over the study period**

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26
27 171 Table 1 highlights the measures to be undertaken at each pre-determined time point.
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29 172 Measurements will be taken daily while receiving the intervention. Patient assessment will also
30
31 173 occur at discharge from hospital and 6 months post discharge.
32
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34 174 In addition to routine blood tests, 20millilitres of blood will be taken from each patient and stored
35
36 175 for later analysis, including the effect of Apolipoprotein E4 (APOE4) status on study outcomes.
37
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39 176 Specimens will be frozen and stored at -80 degrees Celsius in the University of New South Wales
40
41 177 Lowy Biorepository.
42
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47 48 179 **Randomisation and blinding**

49
50 180 Permutated block randomisation will be conducted with a block size of 4 and 25 blocks using a
51

52 181 computer-generated algorithm. An independent clinical trials pharmacist will create the
53

54 182 randomisation schedule which will be provided to the clinical trials pharmacy staff responsible for
55

56 183 production and dispensing of the medication. Each vial of insulin or placebo will be labelled with a
57

58 184 sequentially allocated randomisation number, which will become that patient's study number.
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3 185 Participants, research and ward staff will be blinded to treatment allocation.
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9 187 Intervention

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12 188 Patients will receive 20 international units (IU) of long-acting insulin (detemir) or a placebo of normal
13
14 189 saline intranasally twice daily at 8am and 8pm via a commercially available drug delivery device
15
16 190 (ViaNase delivery device, Kurve Technology, Bothell, Washington). This device has been used
17
18 191 successfully in previous trials of intranasal insulin in cognitive impairment (29, 30). The device will
19
20 192 release 20IU insulin detemir or placebo intranasally via a small nose piece over a 40 second period.
21
22 193 Patients will receive 20 seconds per nostril twice daily and during administration be instructed to
23
24 194 breath normally through the nose.
25
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28

29 195 Following intranasal administration, insulin enters the brain either through direct entry via the
30
31 196 cribriform plate and the olfactory nerves or via specific receptors in the blood-brain barrier or a
32
33 197 combination of the two (42). In 15-30 minutes, insulin peptides are detected within the cerebral
34
35 198 cortex and hippocampus (43). Compared to the subcutaneous route, intranasal administration of
36
37 199 insulin demonstrates an approximately 2000-fold increase in the $AUC_{\text{brain:plasma}}$ ratio, meaning at
38
39 200 similar doses the intranasal route reaches comparable or increased brain insulin concentration but
40
41 201 substantially lower plasma concentration (44).
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45 202 The total daily dose of 40IU of insulin detemir is based on research by Claxton et. al demonstrating
46
47 203 safety and efficacy in older patients with Alzheimer's dementia. In this trial, 60 patients with mild
48
49 204 cognitive impairment or mild-to-moderate AD received either placebo, 20IU of insulin detemir, or
50
51 205 40IU of insulin detemir intranasally for 21 days. Participants receiving 40IU of insulin detemir
52
53 206 demonstrated significant improvements in verbal and visuospatial working memory. No statistically
54
55 207 significant effect was found in the 20IU detemir group. No treatment-related severe adverse events
56
57 208 were reported (45).
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3 209 Pre-prepared, spare vials and in-use devices will be stored between 2-8 degrees Celsius in the ward
4
5 210 medication fridge.

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7
8 211 The medication will be administered by ward registered nurses specifically trained for the trial.

9
10 212 Insulin is considered a "schedule 4" drug meaning two nurses must check the prescription, patient
11
12 213 identity and be present for drug administration. Nurses will record challenges regarding
13
14 214 administration of the intervention, including partially received or omitted doses, in the electronic
15
16 215 patient record which will be reviewed by trial staff daily.

17
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19
20 216 The intervention will cease following two consecutive CAM negative days.

21
22 217 Cessation of treatment with the study intervention will also occur if:

- 23
24 218
- 25 • The patient is discharged from the hospital
 - 26
27 219 • Patient or treating clinician requests discontinuation
 - 28
29 220 • Unacceptable side effects from study medications (defined by National Cancer Institute
30
31 221 Common Criteria for Adverse Events; Common Terminology Criteria for Adverse Events
32
33 222 version 4.0)
 - 34
35 223 • Participants who in the opinion of the investigator are not well enough to continue in the
36
37 224 study
 - 38
39 225 • Adverse events related to the study medicine are unacceptable to the participant/carer or
40
41 226 clinician in charge e.g. symptomatic or severe hypoglycaemia (blood sugar level <3.0mmol/L)
 - 42
43 227 • Treatment is deemed ineffective, defined as no improvement in delirium index over 7 days.
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48 228 Patients withdrawn from the study will be included in statistical analysis on an intention-to-treat
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50 229 basis.

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231 Safety

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

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

242 Adverse events will be assessed daily through participant interview supplemented by review of the
243 electronic medical record. Serious adverse events as defined by the International Conference on
244 Harmonisation Guidelines for Good Clinical Practice will be reported in accordance with local ethics
245 requirements. An independent data and safety monitoring board (DSMB) will oversee the study and
246 meet after each twenty patients. Serious adverse events will be discussed with the lead investigator
247 immediately and reported to the Human Research Ethics Committee (HREC) and trial DSMB within
248 24 hours.

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

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3 254 There are two main scenarios which could prompt DSMB to request termination of the study. Firstly,
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5 255 if there are a significant number of serious adverse events possibly attributed to the intervention
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7 256 leading to patient safety concerns and secondly, significant benefit from the intervention. Should
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9 257 termination of the trial be requested, researchers would be unblinded and data analysis would
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11 258 occur. The HREC and participants would be informed the trial was stopped and reasons for
12
13 259 termination given.
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21 261 **Outcomes**

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23
24 262 The primary and secondary outcomes are outlined in table 1. The primary outcome will be duration
25
26 263 of delirium in days. Delirium assessment will be conducted daily from enrolment until delirium
27
28 264 resolution, defined as two consecutive days (48hours) CAM negative. Patients discharged with
29
30 265 delirium will be followed up daily for up to one week to assess for delirium resolution. Secondary
31
32 266 outcomes will determine if intranasal insulin compared to placebo decreases acute length of hospital
33
34 267 stay, reduces severity of delirium, reduces hospital complications, reduces new admission to nursing
35
36 268 home, decreases mortality and decreases use of antipsychotic medications during an inpatient stay.
37
38 269 Patients will be followed up at 6 months post-discharge to assess if intranasal insulin reduces mortality
39
40 270 and preserves cognition and function. Adherence to the intervention will be measured by percentage
41
42 271 of doses successfully administered.
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50 273 **Sample size**

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53 274 Power analysis (with 5% significance and 80% power) was performed using published data which
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55 275 shows the mean duration of delirium clustered at approximately 8 days in Geriatric medicine ward
56
57 276 populations(50, 51). Power calculation shows reducing delirium duration by two days (from 8 days to
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3 277 6 days) requires 36 in each arm for a total of 72 patients. Allowing for a 30% dropout rate, a total of
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5 278 100 participants will be sought.
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10 11 280 **Statistical Analysis** 12

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15 281 Statistical analysis will be conducted using IBM SPSS Statistics software. An intention-to-treat
16
17 282 approach will be adopted for all analyses and statistical significance assumed at the level of 5%
18
19 283 ($P < 0.05$). Baseline characteristics will be reported for the overall population and separately for each
20
21 284 group.
22

23
24 285 The primary outcome, duration of delirium measured in days, will be analysed first with a Mann
25
26 286 Whitney U test which has high statistical power (52) and then using survival analysis Cox
27
28 287 proportional hazard method including dementia, nursing home status, severity of disease and
29
30 288 comorbidity as covariates. Sensitivity analysis will be conducted using normality-improving data
31
32 289 transformations or Gamma regression with a log link according to the distribution of the primary
33
34 290 outcome. For the major secondary outcome, trajectory of delirium severity measured by the
35
36 291 delirium index over time, a generalised linear mixed model will be used. Binary outcomes like
37
38 292 mortality (in-hospital and at six months) and institutionalisation will be evaluated using a modified
39
40 293 Poisson regression (53). A linear regression will assess possible preservation of function, measured
41
42 294 by Barthel index (54) and modified Instrumental Activities of Daily Living (55), and for all other linear
43
44 295 secondary outcomes. Bootstrapping will be applied if the models fail to satisfy the normality
45
46 296 assumptions. For length of hospital stay, a log-linear or gamma regression with a log link will be
47
48 297 implemented. The number of hospital complications and the use of antipsychotics during
49
50 298 hospitalization will be reported.
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56 299 Subgroup analysis stratifying by age, sex, dementia and APOE status will be conducted.
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300

301 Data Management

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

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

310

311 Patient and public involvement

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

317

318 Discussion

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

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3 324 cognitive and functional impairment (57), with prolonged delirium exposure leading to greater
4
5 325 cerebral damage.

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8 326 To date, there are no trials assessing intranasal insulin as a treatment for delirium, however, it could
9
10 327 improve cognitive and clinical outcomes for delirious patients via a variety of mechanisms. Intranasal
11
12 328 insulin increases cerebral perfusion (32, 58-60) and increases or maintains cerebral glucose
13
14 329 metabolism on FDG-PET (61, 62). In young healthy adults and patients with type II diabetes mellitus,
15
16 330 intranasal insulin enhances functional connectivity within the default mode network, an important
17
18 331 centre for higher cognitive processes in which delirious patients demonstrate dysconnectivity (13, 63,
19
20 332 64). The hypothalamic-pituitary-adrenal (HPA) axis is also insulin responsive and following
21
22 333 administration of intranasal insulin healthy populations demonstrate diminished saliva and plasma
23
24 334 cortisol (31, 65). As aberrant HPA axis activity is hypothesised to contribute to delirium
25
26 335 pathophysiology, modification of this pathway may also lead to improved outcomes (12).

27
28
29 336 We anticipate this trial will be pragmatic, inclusive and representative of real-world Geriatric medicine
30
31 337 inpatients. As such, we will include patients with pre-existing dementia and those residing in
32
33 338 residential aged care facilities. This vulnerable population is at highest risk for delirium yet commonly
34
35 339 under-represented in therapeutic trials.

36
37
38 340 An important aspect of this study will be patient tolerability of an inhaled nasal solution twice daily.
39
40 341 Ward registered nurses administering intranasal insulin will receive training in both administration
41
42 342 and subsequent documentation of the intervention. We will report on adherence and patients will be
43
44 343 analysed on an intention-to-treat basis.

45
46
47 344 As duration of delirium is perhaps the most clinically relevant outcome for both clinicians and patients,
48
49 345 we have chosen this as the primary outcome for the trial. The mean duration of delirium in Geriatric
50
51 346 medicine inpatients has been demonstrated to be 8 +/- 9 days, however, symptoms of delirium can
52
53 347 persist for up to 12 months (50). We anticipate some patients, particularly those returning to high
54
55 348 level care residential aged care facilities, will be discharged with delirium and this group will be

1
2
3 349 followed up daily for up to one week to assess for delirium resolution. Daily assessment after one
4
5 350 week is beyond the allocated resources for this trial.
6
7

8 351 If found to be efficacious, this would lead to multicentre trials to confirm these findings. There would
9
10 352 also be the opportunity to explore intranasal insulin in prevention of delirium and its role across
11
12 353 settings, including in the intensive care and post-operative populations which also represent
13
14 354 vulnerable patient groups.
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17
18 355 Should the intervention reduce the duration of delirium the benefits to patients and their families
19
20 356 could be significant, both in alleviating acute distress and longer-term negative sequelae of delirium.
21
22 357 The treatment also has the potential to save significant financial resources related to both the acute
23
24 358 treatment of delirium and the residual effects with regards to loss of independence and higher care
25
26 359 needs after resolution of delirium. Finally, irrespective of the outcome, this trial will contribute to our
27
28 360 understanding of the pathophysiological mechanisms of delirium particularly the role of impaired
29
30 361 cerebral perfusion and metabolism.
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35 362 **Declarations**

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37 363

38
39 364 **Ethics approval and consent to participate:** The trial methods, protocol and consent procedures
40
41 365 were approved by the South Eastern Sydney Human Research and Ethics Committee (HREC 16_320).
42
43 366 As required by the New South Wales Guardianship act 1987 (part 5), New South Wales Civil and
44
45 367 Administrative Tribunal, approval to conduct this clinical trial has also been obtained (case number
46
47 368 2017/00204946).
48
49
50

51 369 **Consent for publication:** Not applicable.
52
53

54 370 **Availability of data and materials:** Materials including data collection and consent forms can be
55
56 371 accessed by contacting the corresponding author.
57

58 372 **Competing interest:** The authors declare that they have no competing interests.
59
60

1
2
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4
5 374 The Julia Lowy Foundation and the Harry Triguboff Foundation. Award/Grant number not applicable.
6
7 375 The funding bodies have no role in trial design, trial conduct, data management, analysis,
8
9 376 interpretation of the data, writing of the manuscript or decision to publish.

10
11
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13
14 378 **Author contributions:** GC initiated the study and is the trial sponsor. AN, AM and GC designed the
15
16 379 original protocol. JC and MR provided substantial input in study processes and logistics. BTu
17
18 380 provided expertise in the area of Endocrinology. BTo provided extensive guidance on the statistical
19
20 381 analysis. All authors contributed to the writing of the manuscript and approved the final version.

21
22
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25 383 Joanne O'Brien and the Pharmacy and Geriatric Departments for their support. AN is supported
26
27 384 through an Australian Government Research Training Program Scholarship.

28
29
30 385
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32
33 386 **Abbreviations:** AD: Alzheimer's dementia; AUC: area under the curve; APOE: Apolipoprotein E; CAM:
34
35 387 confusion assessment method; CSF: cerebrospinal fluid; DI: delirium index; DSM: Diagnostic and
36
37 388 Statistical Manual of Mental Disorders; DSMB: data and safety monitoring board; FDG-PET:
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39 389 fluorodeoxyglucose positron emission tomography; HPA: hypothalamic-pituitary-adrenal; HREC:
40
41 390 Human Research Ethic Committee; IU: international units; MCI: mild cognitive impairment.

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48 392 Caption for figure 1: Flow of participants through the study.

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For peer review only

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

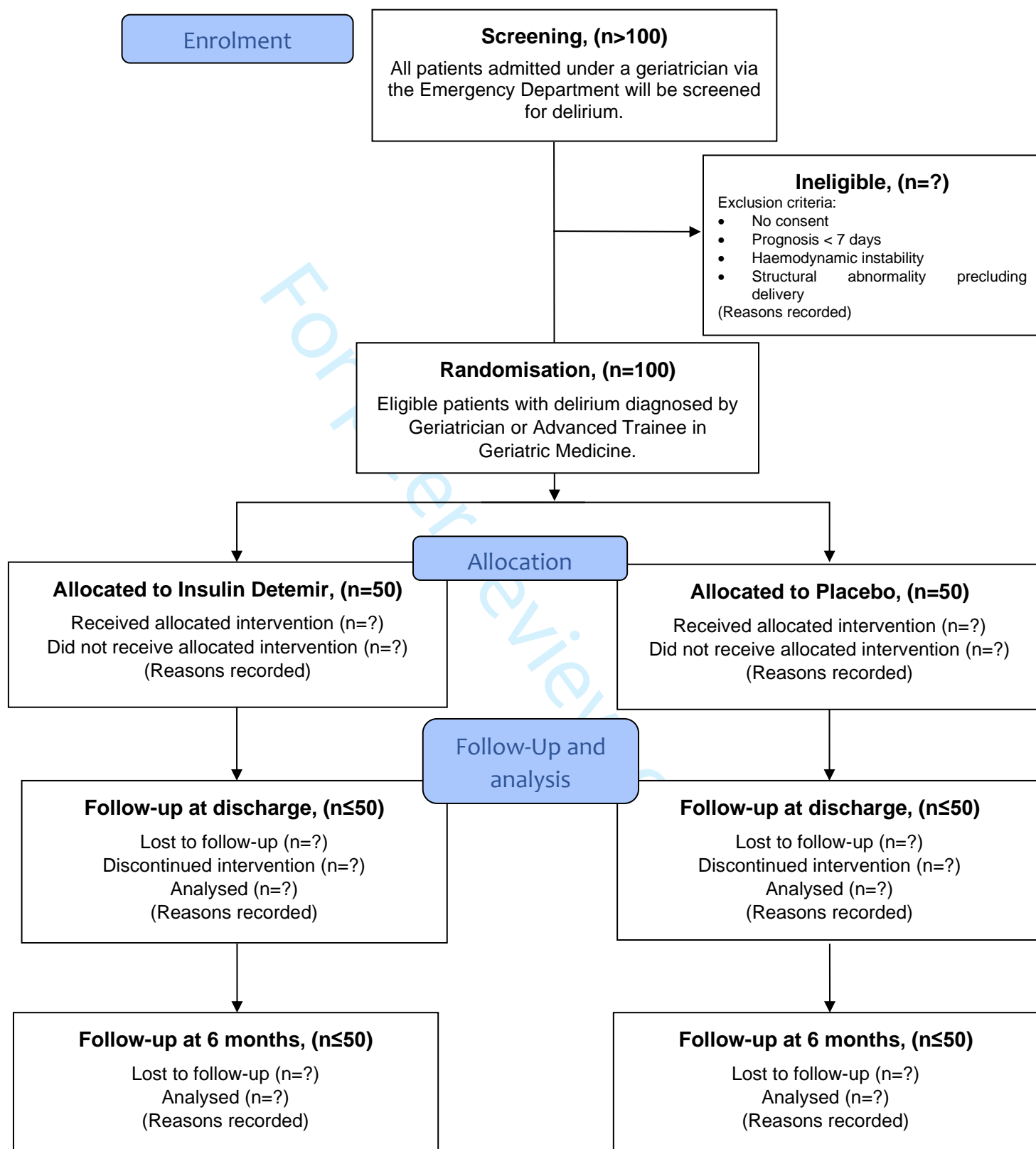
Information collected for all participants	B	D	DC	6M	O
Socio-demographics					
Age, gender, education, occupation, handedness, marital status.	x				
Place of residence and new admission to Residential Aged Care Facility.	x		x	x	S
Medical and functional status					
Medical history, medication use, history 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 II 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 equivalent 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

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Figure 1. CONSORT study flow diagram.



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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

1	Roles and	#5b	Name and contact information for the trial sponsor	16
2	responsibilities:			
3	sponsor contact			
4	information			
5				
6				
7				
8	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	16
9	responsibilities:		collection, management, analysis, and interpretation of data;	
10	sponsor and funder		writing of the report; and the decision to submit the report for	
11			publication, including whether they will have ultimate authority	
12			over any of these activities	
13				
14				
15				
16	Roles and	#5d	Composition, roles, and responsibilities of the coordinating centre,	10, 11,
17	responsibilities:		steering committee, endpoint adjudication committee, data	13
18	committees		management team, and other individuals or groups overseeing the	
19			trial, if applicable (see Item 21a for data monitoring committee)	
20				
21				
22				
23	Introduction			
24				
25	Background and	#6a	Description of research question and justification for undertaking	3, 4, 8-
26	rationale		the trial, including summary of relevant studies (published and	10
27			unpublished) examining benefits and harms for each intervention	
28				
29				
30	Background and	#6b	Explanation for choice of comparators	8
31	rationale: choice of			
32	comparators			
33				
34				
35				
36	Objectives	#7	Specific objectives or hypotheses	5
37				
38	Trial design	#8	Description of trial design including type of trial (eg, parallel	5
39			group, crossover, factorial, single group), allocation ratio, and	
40			framework (eg, superiority, equivalence, non-inferiority,	
41			exploratory)	
42				
43				
44				
45	Methods:			
46	Participants,			
47	interventions, and			
48	outcomes			
49				
50				
51				
52	Study setting	#9	Description of study settings (eg, community clinic, academic	5, 6
53			hospital) and list of countries where data will be collected.	
54			Reference to where list of study sites can be obtained	
55				
56				
57	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable,	6, 7
58			eligibility criteria for study centres and individuals who will	
59				
60				

		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: adherence	#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

1	Allocation concealment	#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
2	mechanism			
3				
4				
5				
6				
7				
8	Allocation:	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6-8
9	implementation			
10				
11	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
12				
13				
14				
15				
16				
17	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10, 11
18	emergency unblinding			
19				
20				
21				
22	Methods: Data			
23	collection,			
24	management, and			
25	analysis			
26				
27				
28				
29	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
30				
31				
32				
33				
34				
35				
36				
37				
38				
39	Data collection plan:	#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
40	retention			
41				
42				
43				
44	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
45				
46				
47				
48				
49				
50				
51	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
52				
53				
54				
55				
56	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12, 13
57	analyses			
58				
59				
60				

1	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	12, 13
2	population and missing		adherence (eg, as randomised analysis), and any statistical methods	
3	data		to handle missing data (eg, multiple imputation)	
4				
5				
6	Methods: Monitoring			
7				
8				
9	Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary of its	11, 13
10	formal committee		role and reporting structure; statement of whether it is independent	
11			from the sponsor and competing interests; and reference to where	
12			further details about its charter can be found, if not in the protocol.	
13			Alternatively, an explanation of why a DMC is not needed	
14				
15				
16				
17	Data monitoring:	#21b	Description of any interim analyses and stopping guidelines,	10, 11
18	interim analysis		including who will have access to these interim results and make	
19			the final decision to terminate the trial	
20				
21				
22	Harms	#22	Plans for collecting, assessing, reporting, and managing solicited	10, 11
23			and spontaneously reported adverse events and other unintended	
24			effects of trial interventions or trial conduct	
25				
26				
27				
28	Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and	10, 11
29			whether the process will be independent from investigators and the	
30			sponsor	
31				
32				
33	Ethics and			
34	dissemination			
35				
36				
37	Research ethics	#24	Plans for seeking research ethics committee / institutional review	6, 16
38	approval		board (REC / IRB) approval	
39				
40				
41	Protocol amendments	#25	Plans for communicating important protocol modifications (eg,	6
42			changes to eligibility criteria, outcomes, analyses) to relevant	
43			parties (eg, investigators, REC / IRBs, trial participants, trial	
44			registries, journals, regulators)	
45				
46				
47	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial	7
48			participants or authorised surrogates, and how (see Item 32)	
49				
50				
51	Consent or assent:	#26b	Additional consent provisions for collection and use of participant	7
52	ancillary studies		data and biological specimens in ancillary studies, if applicable	
53				
54				
55	Confidentiality	#27	How personal information about potential and enrolled participants	13
56			will be collected, shared, and maintained in order to protect	
57			confidentiality before, during, and after the trial	
58				
59				
60				

1	Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
2				
3				
4				
5	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
6				
7				
8				
9				
10	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
11				
12				
13				
14	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
15				
16				
17				
18				
19				
20				
21	Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	14
22				
23				
24				
25	Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	14
26				
27				
28	Appendices			
29				
30				
31	Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	13
32				
33				
34				
35	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
36				
37				
38				
39				

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

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22
23 **Word count:** Abstract = 247 words. Body = 3804

24
25 **Key words:** delirium, treatment, intranasal insulin, older, drug therapy.

26

27 Abstract

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

35 **Methods and analysis:** This is a prospective randomised, placebo-controlled, double blind study with
36 6 months follow up. One hundred patients aged 65 years or older presenting to hospital with delirium
37 admitted under Geriatric Medicine will be recruited. Participants will be randomised to intranasal
38 insulin detemir or placebo administered twice daily until delirium resolves, defined as Confusion
39 Assessment Method (CAM) negative for two days, or discharge from hospital. The primary outcome
40 measure will be duration of delirium using the CAM. Secondary outcome measures will include length
41 of hospital stay, severity of delirium, adherence to treatment, hospital complications, new admission
42 to nursing home, mortality, use of antipsychotic medications during hospital stay and cognitive and
43 physical function at 6-months post-discharge.

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

47 **Trial registration:** ACTRN12618000318280

48 Strengths and Limitations:

49

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

61 Background

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

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

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

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

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

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

1
2
3 98 It is now well established that the brain is an insulin sensitive organ; insulin receptors are widely
4
5 99 expressed in the brain, with greatest saturation in the corticolimbic structures (23). Insulin enhances
6
7 100 learning and memory by modulating neuronal growth, metabolism, plasticity and cholinergic function
8
9
10 101 (23, 24).

11
12 102 The role of glucose metabolism in the pathogenesis of neurodegenerative disease is a growing area of
13
14 103 research (25). Mild Cognitive Impairment (MCI) and Alzheimer's Dementia (AD) have been
15
16 104 characterised as states of brain-specific insulin resistance and deficiency sometimes called "type 3
17
18 105 diabetes" (26). Patients with early stage AD demonstrate pronounced insulin and insulin-like growth
19
20 106 factor deficiency and resistance which progress with severity of neurodegeneration (23).
21
22 107 Administration of intravenous (IV) insulin while maintaining fasting serum glucose levels improves
23
24 108 memory in patients with Alzheimer's Disease (27). However, therapeutic administration of IV insulin
25
26 109 is not feasible or safe due to the substantial risk of systemic hypoglycaemia.

27
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29
30
31 110 The intranasal route of delivery provides a non-invasive and safe means of transporting insulin to the
32
33 111 brain. A recent systematic review identified seven studies (total, N =293) examining the effect of
34
35 112 intranasal insulin on MCI or AD, of which six demonstrated significant improvements in verbal memory
36
37 113 (28). Positive outcomes in functional status were also observed (29-31). Improvements in attention,
38
39 114 visuospatial memory and executive function have also been demonstrated in other populations (32-
40
41 115 34).

42
43
44
45 116 One pilot trial has assessed the effect of intranasal insulin on delirium prevention in a cohort of 21
46
47 117 older cardiothoracic surgical patients (35). The incidence of postoperative delirium was lower in the
48
49 118 intranasal group (18% vs 40%) although the result was not statistically significant, likely due to the
50
51 119 small sample size. No serious adverse events were reported (36).

52
53
54
55 120 Given that intranasal insulin improves cognition as well as cerebral perfusion and metabolism, this
56
57 121 trial will investigate its potential role in treatment of delirium.

1
2
3 122 This randomised controlled trial will evaluate whether intranasal insulin, compared to placebo, can
4
5 123 reduce the duration of delirium in older patients admitted under Geriatric Medicine.
6
7
8

9 124 **Methods**

13 125 **Design**

17 126 This is a single site, randomised, double-blind, placebo-controlled trial of 100 older people diagnosed
18
19 127 with delirium on admission to hospital (prevalent delirium). Figure 1 gives an overview of study
20
21 128 design.
22
23

24 129 This research will be conducted in accordance with the Declaration of Helsinki. As required by the New
25
26 130 South Wales Guardianship act 1987 (part 5), New South Wales Civil and Administrative Tribunal,
27
28 131 approval to conduct this clinical trial has been obtained (case number 2017/00204946). The trial was
29
30 132 registered in the Australian and New Zealand Clinical Trial Registry on 5 March 2018
31
32 133 (ACTRN12618000318280).
33
34

35
36 134
37
38

39 135 **Population**

41
42
43 136 The study population will comprise older people admitted under a Geriatrician at a large tertiary
44
45 137 hospital in metropolitan Sydney, Australia. Potential participants must be a) diagnosed with
46
47 138 prevalent delirium, b) receiving inpatient care on the Geriatric Medicine Wards, c) age > 64 years, d)
48
49 139 have a consenting “person responsible” and e) be enrolled in the trial within 48 hours of admission
50
51 140 to hospital. People with known cognitive impairment and dementia will be included.
52
53

54
55 141 Exclusion criteria include a) people who are haemodynamically unstable (based on treating
56
57 142 physicians judgement guided by activation of a “red zone response” on the NSW Health Standard
58
59 143 Adult General Observation Chart(37)), b) have a predicted life expectancy of less than seven days as
60

1
2
3 144 judged by the admitting geriatrician, c) have an allergy to insulin detemir formulation or d) a
4
5 145 structural abnormality precluding the use of the nasal drug delivery device, e) proven or suspected
6
7 146 COVID-19. People will also be excluded if consent is not obtained or they were previously enrolled in
8
9 147 the trial. Non-English-speaking patients who are unable to participate in cognitive assessments will
10
11 148 also be excluded. The trial will not include patients with incident delirium.
12
13
14
15
16 149

19 150 Screening and Evaluation of delirium

22 151 Within the emergency department or on transfer to the Geriatric Medicine Ward, all patients age
23
24 152 >64 years will be screened by nursing staff for delirium using the Confusion Assessment Method
25
26 153 (CAM) (38, 39). Patients with delirium diagnosed by a Geriatrician or Advanced Trainee in Geriatric
27
28 154 Medicine using the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition criteria (DSM
29
30 155 5) will be considered for the trial (40).

34 156 Study team members will use the CAM to conduct daily delirium assessments between 12-2pm. All
35
36 157 members of the study team will undergo formal training using the CAM. Bedside assessment will be
37
38 158 supplemented by review of the medical records and collateral history from the patient's carer or
39
40 159 ward staff where appropriate. The presence of delirium will be documented using the long form
41
42 160 CAM (38). Delirium severity will be assessed using the Delirium Index (DI) (41). Delirium clinical
43
44 161 subtype will be assessed using the abbreviated version of the Delirium Motor Subtyping Scale
45
46 162 (DMSS-4) (42). A Mini-Mental Status Examination (MMSE) will be used to complete the CAM and DI
47
48 163 during the initial assessment and a standardised structured assessment will be conducted on
49
50 164 subsequent days (see appendix A).

55 165 Interrater reliability using the CAM and DI will be assessed using Cohen's kappa coefficient based on
56
57 166 twenty patient reviews (43).
58
59
60

167

168 Consent

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

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

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

178

179 Assessment over the study period

180 Table 1 highlights the measures to be undertaken at each pre-determined time point.

181 Measurements will be taken daily while receiving the intervention. Patient assessment will also
182 occur at discharge from hospital and 6 months post discharge.

183

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	

9

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 equivalent 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

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

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

1
2
3 187 Dementia status will be determined by a history of dementia diagnosis (informant history and
4
5 188 medical record review) and/or an average IQCODE score >3.44 (44).
6
7

8 189 In addition to routine blood tests, 20millilitres of blood will be taken from each patient and stored
9
10 190 for later analysis, including the effect of Apolipoprotein E4 (APOE4) status on study outcomes.(56)
11
12 191 Specimens will be frozen and stored at -80 degrees Celsius in the University of New South Wales
13
14
15 192 Lowy Biorepository.
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21 194 Randomisation and blinding

22
23
24 195 Permutated block randomisation will be conducted with a block size of 4 and 25 blocks using a
25
26 196 computer-generated algorithm. An independent clinical trials pharmacist will create the
27
28 197 randomisation schedule which will be provided to the clinical trials pharmacy staff responsible for
29
30 198 production and dispensing of the medication. Each vial of insulin or placebo will be labelled with a
31
32 199 sequentially allocated randomisation number, which will become that patient's study number.
33
34

35
36 200 Participants, research and ward staff will be blinded to treatment allocation.
37
38

39 201
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41

42 202 Intervention

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45
46 203 Patients will receive 20 international units (IU) of long-acting insulin (detemir) or a placebo of normal
47
48 204 saline intranasally twice daily at 8am and 8pm via a commercially available drug delivery device
49
50 205 (ViaNase delivery device, Kurve Technology, Bothell, Washington). This device has been used
51
52 206 successfully in previous trials of intranasal insulin in cognitive impairment (30, 31). The device will
53
54 207 release 20IU insulin detemir or placebo intranasally via a small nose piece over a 40 second period.
55
56 208 Patients will receive 20 seconds per nostril twice daily and during administration be instructed to
57
58 209 breath normally through the nose.
59
60

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3 210 Following intranasal administration, insulin enters the brain either through direct entry via the
4
5 211 cribriform plate and the olfactory nerves or via specific receptors in the blood-brain barrier or a
6
7 212 combination of the two (57). In 15-30 minutes, insulin peptides are detected within the cerebral
8
9 213 cortex and hippocampus (58). Compared to the subcutaneous route, intranasal administration of
10
11 214 insulin demonstrates an approximately 2000-fold increase in the $AUC_{\text{brain:plasma}}$ ratio, meaning at
12
13 215 similar doses the intranasal route reaches comparable or increased brain insulin concentration but
14
15 216 substantially lower plasma concentration (59).

16
17
18
19 217 The total daily dose of 40IU of insulin detemir is based on research by Claxton et. al demonstrating
20
21 218 safety and efficacy in older patients with Alzheimer's dementia. In this trial, 60 patients with mild
22
23 219 cognitive impairment or mild-to-moderate AD received either placebo, 20IU of insulin detemir, or
24
25 220 40IU of insulin detemir intranasally for 21 days. Participants receiving 40IU of insulin detemir
26
27 221 demonstrated significant improvements in verbal and visuospatial working memory. No statistically
28
29 222 significant effect was found in the 20IU detemir group. No treatment-related severe adverse events
30
31 223 were reported (56).

32
33
34
35 224 Pre-prepared, spare vials and in-use devices will be stored between 2-8 degrees Celsius in the ward
36
37 225 medication fridge.

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40
41 226 The medication will be administered by ward registered nurses specifically trained for the trial.
42
43 227 Nurses will record challenges regarding administration of the intervention, including partially
44
45 228 received or omitted doses, in the electronic patient record which will be reviewed by trial staff daily.

46
47
48 229 The intervention will cease following two consecutive CAM negative days; this criteria has been
49
50 230 successfully adopted in other studies assessing delirium duration.(60) The intervention will be
51
52 231 discontinued for patients with subsyndromal delirium (defined by the presence of one or more CAM
53
54 232 symptoms without meeting the criteria for delirium) (61).

55
56
57 233 Cessation of treatment with the study intervention will also occur if:
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59 234

- The patient is discharged from the hospital

- 1
2
3 235 • Patient or treating clinician requests discontinuation
4
5 236 • Unacceptable side effects from study medications (defined by National Cancer Institute
6
7 Common Criteria for Adverse Events; Common Terminology Criteria for Adverse Events
8 237
9 version 4.0)
10 238
11
12 239 • Participants who in the opinion of the investigator are not well enough to continue in the
13
14 study
15 240
16
17 241 • Adverse events related to the study medicine are unacceptable to the participant/carer or
18
19 clinician in charge e.g. symptomatic or severe hypoglycaemia (blood sugar level <3.0mmol/L)
20 242
21 243 • Treatment is deemed ineffective, defined as no improvement in delirium index over 7 days.
22
23

24 244 Patients withdrawn from the study will be included in statistical analysis on an intention-to-treat
25
26 245 basis.
27

28
29 246 If delirium recurs after resolution of the initial episode (i.e. hospital acquired delirium) the
30
31 247 intervention will not be recommenced.
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37 249 Safety

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41 250 Studies have demonstrated that less than 3% of intranasally-delivered insulin is detectable in the
42
43 251 serum and as a result intranasal insulin has a negligible risk of hypoglycaemia (28, 62). A systematic
44
45 252 review on the safety of intranasal insulin included 38 studies (N=1092) and found no cases of
46
47 253 hypoglycaemia or severe adverse events (63). The most commonly reported side effects were
48
49 254 transient and local to the nasal area including nasal tingling and burning, less commonly rhinitis and
50
51 255 nasal bleeding occurred.
52
53

54
55 256 Although the risk of hypoglycaemia is largely theoretical, blood glucose levels will be measured at
56
57 257 baseline and four times daily during the study intervention (07:00, 13:00, 19:00, 22:00). As adequate
58
59
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1
2
3 258 and uninterrupted sleep is a core principle in delirium management and disturbed sleep can
4
5 259 precipitate or exacerbate delirium, blood glucose levels will not be taken overnight.
6
7

8 260 Adverse events will be assessed daily through participant interview supplemented by review of the
9
10 261 electronic medical record. Serious adverse events as defined by the International Conference on
11
12 262 Harmonisation Guidelines for Good Clinical Practice will be reported in accordance with local ethics
13
14 263 requirements. An independent data and safety monitoring board (DSMB) will oversee the study and
15
16 264 meet after each twenty patients. Serious adverse events will be discussed with the lead investigator
17
18 265 immediately and reported to the Human Research Ethics Committee (HREC) and trial DSMB within
19
20 266 24 hours.
21
22
23

24 267 Delirium is associated with a high in-hospital mortality rate, previously demonstrated to reach 35% in
25
26 268 an older population (64). As such, a key role of DSMB will be to review all deaths and serious adverse
27
28 269 events in detail to determine if the adverse event was in keeping with the natural history of the illness
29
30 270 or could be attributed to the study intervention (65). Should concerns arise regarding patient safety
31
32 271 the DSMB may request to unblind for decision making purposes.
33
34
35

36 272 There are two main scenarios which could prompt DSMB to request termination of the study. Firstly,
37
38 273 if there are a significant number of serious adverse events possibly attributed to the intervention
39
40 274 leading to patient safety concerns and secondly, significant benefit from the intervention. Should
41
42 275 termination of the trial be requested, researchers would be unblinded and data analysis would
43
44 276 occur. The HREC and participants would be informed the trial was stopped and reasons for
45
46 277 termination given.
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53 279 Outcomes

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57 280 The primary and secondary outcomes are outlined in table 1. The primary outcome will be duration
58
59 281 of delirium in days. Delirium assessment will be conducted daily from enrolment until delirium
60

1
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3 282 resolution, defined as two consecutive days (48hours) CAM negative. Patients discharged with
4
5 283 delirium will be followed up in person daily for up to one week to assess for delirium resolution.
6
7 284 Secondary outcomes will determine if intranasal insulin compared to placebo decreases acute length
8
9 285 of hospital stay, reduces severity of delirium, reduces hospital complications, reduces new admission
10
11 286 to nursing home, decreases mortality and decreases use of antipsychotic medications during an
12
13 287 inpatient stay. Patients will be followed up at 6 months post-discharge to assess if intranasal insulin
14
15 288 reduces mortality and preserves cognition and function. Adherence to the intervention will be
16
17 289 measured by percentage of doses successfully administered.
18
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23 24 291 **Sample size**

25
26
27 292 Power analysis (with 5% significance and 80% power) was performed using published data which
28
29 293 shows the mean duration of delirium clustered at approximately 8 days in Geriatric medicine ward
30
31 294 populations(66, 67). Power calculation shows reducing delirium duration by two days (from 8 days to
32
33 295 6 days) requires 36 in each arm for a total of 72 patients. Allowing for a 30% dropout rate, a total of
34
35 296 100 participants will be sought.
36
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43 298 **Statistical Analysis**

44
45
46 299 Statistical analysis will be conducted using IBM SPSS Statistics software. An intention-to-treat
47
48 300 approach will be adopted for all analyses and statistical significance assumed at the level of 5%
49
50 301 ($P<0.05$). Baseline characteristics will be reported for the overall population and separately for each
51
52 302 group.
53
54
55

56 303 The primary outcome, duration of delirium measured in days, will be analysed first with a Mann
57
58 304 Whitney U test which has high statistical power (68) and then using survival analysis Cox
59
60

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3 305 proportional hazard method including dementia, nursing home status, severity of acute illness
4
5 306 (APACHE III) and comorbidity as covariates. Sensitivity analysis will be conducted using normality-
6
7 307 improving data transformations or Gamma regression with a log link according to the distribution of
8
9 308 the primary outcome. Analysis will include in hospital death as a competing risk. For the major
10
11 309 secondary outcome, trajectory of delirium severity measured by the delirium index over time, a
12
13 310 generalised linear mixed model will be used. Binary outcomes like mortality (in-hospital and at six
14
15 311 months) and institutionalisation will be evaluated using a modified Poisson regression (69). A linear
16
17 312 regression will assess possible preservation of function, measured by Barthel index (45) and
18
19 313 modified Instrumental Activities of Daily Living (46), and for all other linear secondary outcomes.
20
21 314 Bootstrapping will be applied if the models fail to satisfy the normality assumptions. For length of
22
23 315 hospital stay, a log-linear or gamma regression with a log link will be implemented. The number of
24
25 316 hospital complications and the use of antipsychotics during hospitalization will be reported.
26
27
28
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30 317 Subgroup analysis stratifying by age, sex, dementia and APOE status will be conducted.
31
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34 318

319 Data Management

320 Data will be collected by trained researchers and stored on a password protected database. One
321 researcher will be responsible for data entry while another member of the study team will monitor
322 the accuracy of data by cross-checking a random 10% sample of subjects.
323
324 Paper files of individual records will be stored in a locked cabinet in a secure location accessible to
325 authorised members of the study team only. Electronic data will be entered in a de-identified format
326 and stored on a password-protected secure server. The complete data set will be stored on the
327 University of New South Wales Data Archive and will be made available at the completion of the trial
328 on reasonable request.

329 Patient and public involvement

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

332

333 Ethics and dissemination:

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

339

340 Discussion

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

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

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3 352 intranasal insulin enhances functional connectivity within the default mode network, an important
4
5 353 centre for higher cognitive processes in which delirious patients demonstrate dysconnectivity (14, 77,
6
7 354 78). The hypothalamic-pituitary-adrenal (HPA) axis is also insulin responsive and following
8
9 355 administration of intranasal insulin healthy populations demonstrate diminished saliva and plasma
10
11 356 cortisol (32, 79). As aberrant HPA axis activity is hypothesised to contribute to delirium
12
13 357 pathophysiology, modification of this pathway may also lead to improved outcomes (13).

14
15
16
17 358 We anticipate this trial will be pragmatic, inclusive and representative of real-world Geriatric medicine
18
19 359 inpatients. As such, we will include patients with pre-existing dementia and those residing in
20
21 360 residential aged care facilities. This vulnerable population is at highest risk for delirium yet commonly
22
23 361 under-represented in therapeutic trials.

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25
26
27 362 An important aspect of this study will be patient tolerability of an inhaled nasal solution twice daily.
28
29 363 Ward registered nurses administering intranasal insulin will receive training in both administration
30
31 364 and subsequent documentation of the intervention. We will report on adherence and patients will be
32
33 365 analysed on an intention-to-treat basis.

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35
36 366 As duration of delirium is perhaps the most clinically relevant outcome for both clinicians and patients,
37
38 367 we have chosen this as the primary outcome for the trial. The mean duration of delirium in Geriatric
39
40 368 medicine inpatients has been demonstrated to be 8 +/- 9 days, however, symptoms of delirium can
41
42 369 persist for up to 12 months (66). We anticipate some patients, particularly those returning to high
43
44 370 level care residential aged care facilities, will be discharged with delirium and this group will be
45
46 371 followed up daily for up to one week to assess for delirium resolution. Daily assessment after one
47
48 372 week is beyond the allocated resources for this trial.

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53 373 If found to be efficacious, this would lead to multicentre trials to confirm these findings. There would
54
55 374 also be the opportunity to explore intranasal insulin in prevention of delirium and its role across
56
57 375 settings, including in the intensive care and post-operative populations which also represent
58
59 376 vulnerable patient groups.

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3 377 Should the intervention reduce the duration of delirium the benefits to patients and their families
4
5 378 could be significant, both in alleviating acute distress and longer-term negative sequelae of delirium.
6
7 379 The treatment also has the potential to save significant financial resources related to both the acute
8
9 380 treatment of delirium and the residual effects with regards to loss of independence and higher care
10
11 381 needs after resolution of delirium. Finally, irrespective of the outcome, this trial will contribute to our
12
13 382 understanding of the pathophysiological mechanisms of delirium particularly the role of impaired
14
15 383 cerebral perfusion and metabolism.
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20 384 **Declarations**

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23
24 386 **Ethics approval and consent to participate:** The trial methods, protocol and consent procedures
25
26 387 were approved by the South Eastern Sydney Human Research and Ethics Committee (HREC 16_320).
27
28 388 As required by the New South Wales Guardianship act 1987 (part 5), New South Wales Civil and
29
30 389 Administrative Tribunal, approval to conduct this clinical trial has also been obtained (case number
31
32 390 2017/00204946).
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36 391 **Consent for publication:** Not applicable.
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39 392 **Availability of data and materials:** Materials including data collection and consent forms can be
40
41 393 accessed by contacting the corresponding author.
42

43 394 **Competing interest:** The authors declare that they have no competing interests.
44

45 395 **Funding:** This trial is financially supported by the JJ Mason and HS Williams Memorial Foundation,
46
47 396 The Julia Lowy Foundation and the Harry Triguboff Foundation. Award/Grant number not applicable.
48
49 397 The funding bodies have no role in trial design, trial conduct, data management, analysis,
50
51 398 interpretation of the data, writing of the manuscript or decision to publish.
52
53

54 399 **Disclosures:** MA receives delirium clinical trial funding from Cancer Australia.
55

56
57 400 **Author contributions:** GC initiated the study and is the trial sponsor. AN, AM and GC designed the
58
59 401 original protocol. JC and MA provided substantial input in study processes and logistics. BTu
60

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

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407

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

413

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

415

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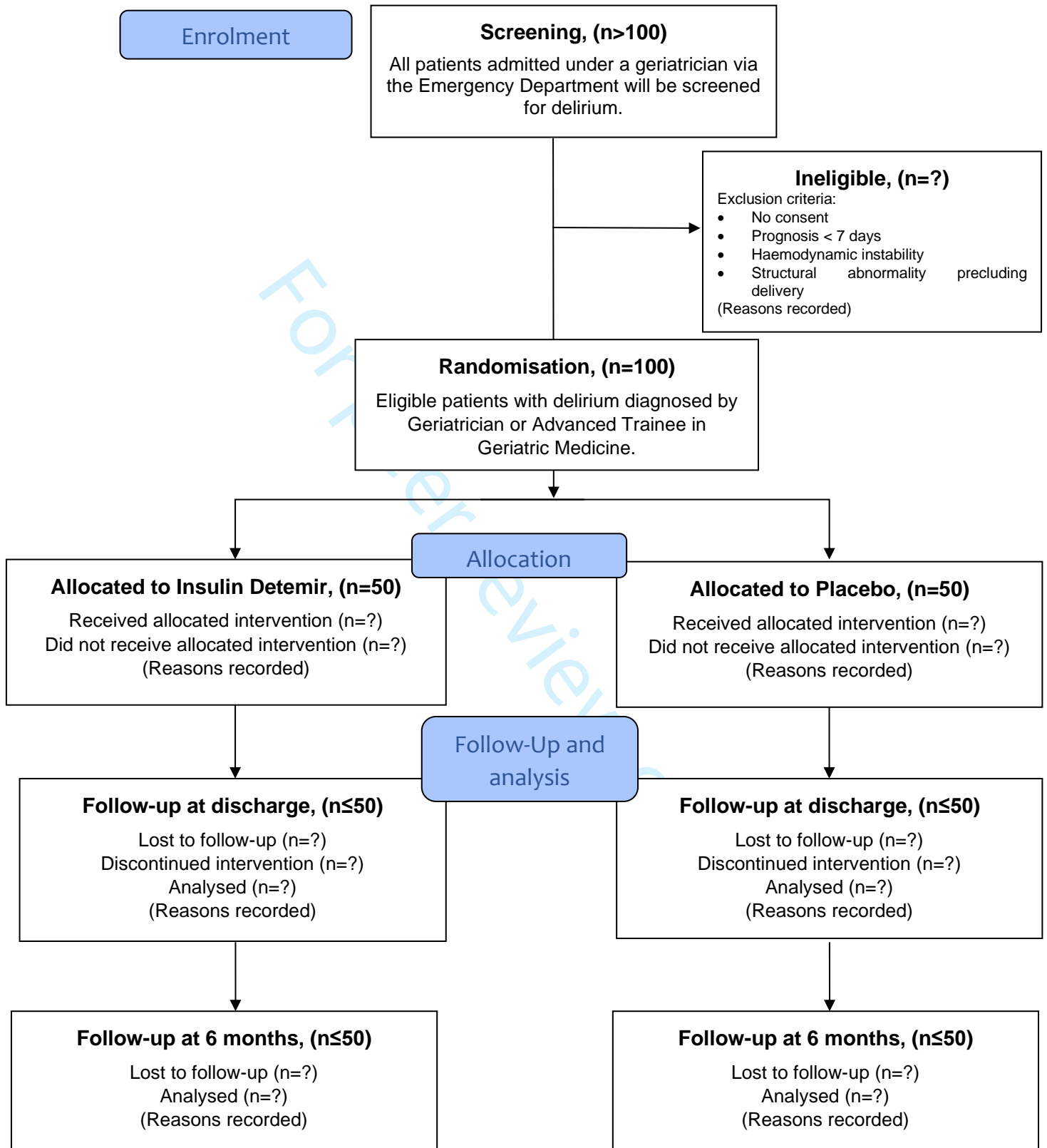
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Figure 1. CONSORT study flow diagram.



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 form 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 SPIRIT reporting 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

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

1	Trial registration	#2a	Trial identifier and registry name. If not yet registered,	2
2				
3				
4			name of intended registry	
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6	Trial registration:	#2b	All items from the World Health Organization Trial	6,7
7				
8	data set		Registration Data Set	
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11				
12	Protocol version	#3	Date and version identifier	N/A
13				
14				
15	Funding	#4	Sources and types of financial, material, and other	17
16				
17			support	
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19				
20	Roles and	#5a	Names, affiliations, and roles of protocol contributors	1, 17
21				
22	responsibilities:			
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24	contributorship			
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28	Roles and	#5b	Name and contact information for the trial sponsor	17
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30	responsibilities:			
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32	sponsor contact			
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34	information			
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37				
38	Roles and	#5c	Role of study sponsor and funders, if any, in study	17
39				
40	responsibilities:		design; collection, management, analysis, and	
41				
42	sponsor and funder		interpretation of data; writing of the report; and the	
43				
44			decision to submit the report for publication, including	
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46			whether they will have ultimate authority over any of	
47				
48			these activities	
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52	Roles and	#5d	Composition, roles, and responsibilities of the	11, 12,
53				
54	responsibilities:		coordinating centre, steering committee, endpoint	14
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56	committees		adjudication committee, data management team, and	
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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

1	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
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11	Interventions:	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9,10
12				
13	description			
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19	Interventions:	#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
20				
21	modifications			
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29	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	11-12
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31	adherence			
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36	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
37				
38	concomitant care			
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42	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
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1	Participant timeline	#13	Time schedule of enrolment, interventions (including any	table 1
2			run-ins and washouts), assessments, and visits for	
3			participants. A schematic diagram is highly	
4			recommended (see Figure)	
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11	Sample size	#14	Estimated number of participants needed to achieve	12
12			study objectives and how it was determined, including	
13			clinical and statistical assumptions supporting any	
14			sample size calculations	
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21	Recruitment	#15	Strategies for achieving adequate participant enrolment	7
22			to reach target sample size	
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26	Methods:			
27				
28	Assignment of			
29	interventions (for			
30	controlled trials)			
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36	Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	8
37	generation		computer-generated random numbers), and list of any	
38			factors for stratification. To reduce predictability of a	
39			random sequence, details of any planned restriction (eg,	
40			blocking) should be provided in a separate document that	
41			is unavailable to those who enrol participants or assign	
42			interventions	
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53	Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	8,9
54	concealment		central telephone; sequentially numbered, opaque,	
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58	mechanism			

sealed envelopes), describing any steps to conceal the sequence until interventions are assigned

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6	Allocation:	#16c Who will generate the allocation sequence, who will enrol	6-9
7			
8	implementation	participants, and who will assign participants to	
9		interventions	
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13	Blinding (masking)	#17a Who will be blinded after assignment to interventions (eg,	9
14		trial participants, care providers, outcome assessors,	
15		data analysts), and how	
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21	Blinding (masking):	#17b If blinded, circumstances under which unblinding is	11,12
22			
23	emergency	permissible, and procedure for revealing a participant's	
24		allocated intervention during the trial	
25	unblinding		
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28	Methods: Data		
29			
30	collection,		
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32	management, and		
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34	analysis		
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38	Data collection plan	#18a Plans for assessment and collection of outcome,	table 1,
39		baseline, and other trial data, including any related	14
40		processes to promote data quality (eg, duplicate	
41		measurements, training of assessors) and a description	
42		of study instruments (eg, questionnaires, laboratory tests)	
43		along with their reliability and validity, if known.	
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45		Reference to where data collection forms can be found, if	
46		not in the protocol	
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1	Data collection plan:	#18b	Plans to promote participant retention and complete	8, 13
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3	retention		follow-up, including list of any outcome data to be	
4			collected for participants who discontinue or deviate from	
5			intervention protocols	
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11	Data management	#19	Plans for data entry, coding, security, and storage,	13
12			including any related processes to promote data quality	
13			(eg, double data entry; range checks for data values).	
14			Reference to where details of data management	
15			procedures can be found, if not in the protocol	
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23	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary	13
24			outcomes. Reference to where other details of the	
25			statistical analysis plan can be found, if not in the	
26			protocol	
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33	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and	13
34	analyses		adjusted analyses)	
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39	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	13
40	population and		adherence (eg, as randomised analysis), and any	
41	missing data		statistical methods to handle missing data (eg, multiple	
42			imputation)	
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48	Methods: Monitoring			
49				
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51	Data monitoring:	#21a	Composition of data monitoring committee (DMC);	11, 13
52	formal committee		summary of its role and reporting structure; statement of	
53			whether it is independent from the sponsor and	
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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

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10	Data monitoring:	#21b	Description of any interim analyses and stopping
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12	interim analysis		guidelines, including who will have access to these
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14			interim results and make the final decision to terminate
15			the trial
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20	Harms	#22	Plans for collecting, assessing, reporting, and managing
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22			solicited and spontaneously reported adverse events and
23			
24			other unintended effects of trial interventions or trial
25			conduct
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30	Auditing	#23	Frequency and procedures for auditing trial conduct, if
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32			any, and whether the process will be independent from
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34			investigators and the sponsor
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38	Ethics and		
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40	dissemination		
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43	Research ethics	#24	Plans for seeking research ethics committee / institutional
44			
45	approval		review board (REC / IRB) approval
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48	Protocol	#25	Plans for communicating important protocol modifications
49			
50	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to
51			
52			relevant parties (eg, investigators, REC / IRBs, trial
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54			participants, trial registries, journals, regulators)
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1	Consent or assent	#26a	Who will obtain informed consent or assent from potential	7-8
2			trial participants or authorised surrogates, and how (see	
3			Item 32)	
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9	Consent or assent:	#26b	Additional consent provisions for collection and use of	7-8
10	ancillary studies		participant data and biological specimens in ancillary	
11			studies, if applicable	
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16	Confidentiality	#27	How personal information about potential and enrolled	14
17			participants will be collected, shared, and maintained in	
18			order to protect confidentiality before, during, and after	
19			the trial	
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26	Declaration of	#28	Financial and other competing interests for principal	16-17
27	interests		investigators for the overall trial and each study site	
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32	Data access	#29	Statement of who will have access to the final trial	14
33			dataset, and disclosure of contractual agreements that	
34			limit such access for investigators	
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39	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care, and for	table 1
40	trial care		compensation to those who suffer harm from trial	
41			participation	
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47	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial	14
48	trial results		results to participants, healthcare professionals, the	
49			public, and other relevant groups (eg, via publication,	
50			reporting in results databases, or other data sharing	
51			arrangements), including any publication restrictions	
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1	Dissemination policy: #31b	Authorship eligibility guidelines and any intended use of	14
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3	authorship	professional writers	
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6	Dissemination policy: #31c	Plans, if any, for granting public access to the full	14
7			
8	reproducible	protocol, participant-level dataset, and statistical code	
9			
10	research		
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14	Appendices		
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17	Informed consent	#32 Model consent form and other related documentation	attached
18			
19	materials	given to participants and authorised surrogates	
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23	Biological specimens	#33 Plans for collection, laboratory evaluation, and storage of	8
24			
25		biological specimens for genetic or molecular analysis in	
26			
27		the current trial and for future use in ancillary studies, if	
28			
29		applicable	
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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](#)