Author's response to reviews

Title: The Oslo Study of Clonidine in Elderly Patients with Delirium; LUCID. The protocol of LUCID

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Author's response to reviews: see over
Thank you for your very thorough and relevant comments; they have greatly improved our manuscript.

The study has been approved by the Regional Ethics Committee and the Norwegian Medicines Agency and is registered in Eudra-CT and ClinicalTrials.gov. We are actively including patients and our answers will take use of some of our relevant experiences so far.

Below we have responded point-by-point to the comments, also describing the subsequent revisions of the manuscript (marked as underlined). We have tried not to expand the manuscript too much, and you find most information and discussions in this cover letter.

Additional Editorial Comments:
"We are concerned regarding the question of sample size, and that we are expecting a thorough reply to the fact that this study may not be sufficient to answer the research question."

Choice of primary endpoint and statistical methods in treatment studies for delirium is not obvious. The natural trajectory of delirium varies greatly and the course is by definition fluctuating. It is also difficult to decide what is a clinically relevant treatment effect. If a "new" treatment should be recommended in this elderly, frail population, the effect should be of a certain size to justify adding yet another drug to the list.

"Standard statistical analysis" looking at, say, either days-to-resolution alone or maximum severity alone, would make it difficult to achieve sufficiently high power. These entities might also not represent the complex condition of delirium.

Accordingly, we have chosen a more "global" approach, looking at the delirium trajectory with mixed linear models. This makes it possible to use all available data - even if some data should be missing. These methods will increase the power of the study. In the manuscript (line 367-378) we have specified our statistical considerations and argue why we consider the sample size as sufficient. [1]

Reviewer 1: Rajesh Tampi
Reviewer's report: No revisions suggested

Reviewer 2: Eamonn Eeles
Reviewer's report with point-by-point response:

Outlined is a study protocol for a planned RCT of clonidine in delirium. The study is novel yet extends logically from existing literature, is methodologically sound, of great clinical relevance and well written. The study is adequately designed to answer the primary and secondary research questions, is sufficiently detailed to allow replication of this work and would appear to adhere to reporting standards. I have some constructive considerations that would render this article suitable for publication once they are sufficiently rectified.

1) Abstract: study outcomes it may be clearer to state trajectory of delirium here Discretionary Revisions

We agree and have changed the manuscript accordingly, line 42.
2) Laboratory tests and blood samples: paragraph 2 There is no control group but I think it very reasonable (as the authors have only alluded to) that the patients can be used as their own controls (before delirium for hospital acquired and after delirium). On that basis it should be possible to interrogate for biomarkers that are pivotal to any potential mechanistic underpinnings of the impact of clonidine (such as is stated by the authors: cortisol and aberrant stress response). Minor Essential Revisions

Because this primarily is a treatment study we chose not to include a delirium-free control group, as it would increase the study-size and financial burden too much. We believe that even without a control group, many interesting biomarkers can be explored in this patient group. Since we sample repeatedly we can explore the course of the markers, and with a 4-month follow-up we can explore possible prognostic features. The consent is wide and open in regard to the use of these samples in the future.

3) Pharmacokinetics of clonidine: paragraph 1 Is consideration given to possible altered CNS permeability and impaired enzymes of drug metabolism in delirium when arriving at the dosing schedule for a drug that is cleared by the liver? Minor Essential Revisions

CNS permeability might be altered in delirium [2], affecting the availability of clonidine in the brain. However, clonidine in any circumstance traverse the blood-brain-barrier, and the anti-hypertensive effect is primarily through central mechanisms. Closely monitoring of BP is thus a monitoring of clonidine’s central effects. We have found no litterature on impaired enzymes of drug metabolism in delirium, and in particular not reagarding clonidine. A step-wise dosing regimen with close monitoring of hemodynamic effects is in our opinion a reasonable and clinically relevant way of dealing with this pharmacokinetic uncertainty.

4) Clinical experience with clonidine: paragraph 2 (less than) 50% side-effects in healthy elderly extrapolates to potentially what in the non-delirious elderly? Do the authors think that enough safeguards are in place for what might be common and innocuous side-effects in the young to unwell older patients? Major Compulsory Revisions

It is difficult to extrapolate the expected proportion of mild side effects to our elderly population. We agree that side effects that seem innocuous for the young population might have greater impact in the frail elderly.

Our safety measures are comprehensive. Not only do the nurses always evaluate BP and pulse before administering the study drug. They also always consider whether the patient is able to swallow the study drug; taking into account drowsiness etc. Further, the patient is examined every day by a physician who not only evaluates the trajectory of delirium, but also the consciousness (with RASS and OSLA) and the presence of side effects (dizziness, symptoms of orthostatic hypotension/bradycardia, mouth dryness, constipation etc). All this is to justify the decision of whether or not the patient can continue with the study drug.

Particularly vulnerable patients (eg terminal patients), where the everyday quality of life is of particular importance, are not included (see exclusion criteria). Clonidine was previously used in higher doses and longer time, also for elderly people (see background). Our treatment is for a maximum of 7 days and only while the patient is at the hospital ward. We regard our practice as safe.

See changes "Monitoring and safety"
5) On the same grounds, given the likely propensity for CNS ischaemia causing delirium in some cases, which may be modified by clonidine, clinical and radiological exclusion of stroke disease (Hachinski index/CT scan respectively) would be a consideration. Discretionary Revisions

One of our exclusion criteria is "Ischemic stroke within the last 3 months". This is assessed both by medical history and the clinical evaluation of the current cause of admission (done both of the treating physician and the study physician). If any doubt exists, the patient will not be included. MR scans will be performed when indicated. Due to the low sensitivity of CT scans to detect ischemic strokes, we do not consider mandatory CT scans as an appropriate safety measure.

The Hachinski index might be useful in separating vascular dementia from degenerative dementia [3] and in that situation it also correlates well with cerebral blood flow. But it is to our knowledge not valid to assess cerebral blood flow in patients with delirium.

6) Safety review: paragraph 1 Will the safety review be undertaken by an independent committee and this should be specified? Minor Essential Revisions

Yes, see change in manuscript, line 179

7) Screening: paragraph 1 The screening programme seems pragmatic and whilst individual components may be suitable (the SQID) this is not the case in combination and should be qualified in its current form. Also, whilst the SQID seems a very ergonomic screening instrument its validation has hitherto not been conducted in the acute care setting. Discretionary Revisions

The screening procedure was designed to provide a pragmatic set of methods to identify patients with delirium, rather than to be a formal package of measures. The components chosen were designed to provide multiple opportunities for picking up delirium without having to do a full diagnostic assessment on all patients. We are looking for patients who are likely to have delirium rather than needing to get all those who might have delirium – so the combination of measures we are using is aimed at that.

Days of the week backwards is a specific rather than a sensitive test. Months of the year backwards is more sensitive to delirium but also more sensitive to dementia. We thus believe that days of the week backward is a good choice to detect clear delirium.

Regarding the SQID – this is really just a form of the 'acute change' criterion that is present in all diagnostic criteria for delirium. The SQID will thus be used as a guide to help address this criterion, but we will also use other methods to look at acute change (as mentioned).

Our screening programme is quite similar to the one used in the recently published study of delirium prevalence in an Irish hospital [4].

The most important factor of the screening process is probably that the study physicians are present at the ward on every weekday evaluating all new patients in regard to the selection criteria of our study. This evaluation is done partly in dialogue with the treating personnel (doctors/nurses) to rule out all patients with known exclusion criteria (no need to bother them with our study-related screening procedures if it is clear they can not join the study). We actively ask the personnel for any delirium symptoms and in cooperation we make sure care-givers are questioned for any change (SQID) and attentions tests are performed (by study physician). Any possible candidates are thoroughly evaluated by the study physicians according to the DSM-5 criteria.
8) Diagnosis of delirium and subsyndromal delirium: paragraph 2 There would seem to be more suitable diagnostic and severity tools (such as the DRS-R-98) for this population than the MDAS (more in keeping with palliative care). Discretionary Revisions

DRS-R-98 does have some advantages to MDAS, in particular the combination of being both a diagnostic tool and severity scale. But as we chose to use the DSM-5-criteria directly, the diagnostic part of this tool is not needed in our study. Also, the DRS-R-98 does not exist in a validated Norwegian translation.

Indeed, the MDAS performs well with a brief training package [5], whereas the DRS-R98 is designed to be used by psychiatrists and/or after more extensive training. Moreover, the MDAS is widely used in delirium research, including in research trials, eg [6].

9) Study medication Is the capsule manageable and tolerable as a medication in a delirious patient/dementia (are there any swallowing issues with this?) Minor Essential Revisions

Our experience so far is that the capsule seems to be manageable and tolerable to our patients. Unability to take oral medication is an exclusion criterion. (Clonidine can be administered as a patch, but unfortunately it was not feasible for us to make a patch placebo for this study. It may however be a very interesting administration form in the future if clonidine shows to have effect on delirium!)

10) Monitoring and safety: paragraph 1 As one of the side-effects is being sleepy and drowsy on standing then there may be a significant risk with this study that is not evident on ICU trials of similar acting drugs (where in the management of sedated supine patients this will not be a concern). A delirious, impulsive and mobile patient may not tolerate dizziness and drowsiness with falls or injury a result. How will this be considered, measured and mitigated against for the purposes of the study? Similarly, how will non-adherence to the haemodynamic monitoring (which will be likely) be considered? Major Compulsory Revisions

We agree it is very important to take this into account. As mentioned, we have chosen a dosage expected to be well tolerated even in this elderly population [7-10] and the dosage is considerably lower than doses used for sedation in the ICU or for treating hypertension.

All the patients are in-hospital and well monitored. Delirious patients with hyperactive and uncritical behaviour will usually have a one-to-one nurse, even at night. The geriatric ward has a falls prevention programme for all patients.

Drowsiness is evaluated daily by physician (with RASS and OSLA) to consider further treatment. Nurses always consider if the patient is adequately awake to be able to take the next dose. We look for symptoms of orthostatic hypotension. Patients at risk of falling are mobilised under observation of trained nurses or physiotherapists.

Measurement of blood-pressure and pulse before every new dose is mandatory. If this is not possible, the dose will not be given.

The study is approved by Norwegian Medicines Agency.

11) Data collection: paragraph 3 I can see no rationale for the inclusion of grip strength unless combined with other performance related tests to look at frailty phenotype? Minor Essential
Revisions

Frailty is a complex geriatric term with no consensus to its definition. Some argue it is practical to "count frailty indicators". We collect data to describe some aspects of frailty.

12) Follow-up assessments: paragraph 2 What is late toxicity of clonidine anticipated and how will it be screened for? Discretionary Revisions

The only "late toxicity" relevant for our study of clonidine is "clonidine withdrawal syndrome" (mainly a rebound effect within 1-2 days after withdrawal of clonidine). Such an effect will give a rise in pulse and BP. With a maximum of only 7 days treatment, such reactions are considered very unlikely.

An adjusted procedure for follow-up is described in the manuscript, line 332-341.

13) Other points for clarification: The authors mention the importance of identifying risk factors for delirium. If this is required then nutrition and sensory impairment should also be included in measurement. Discretionary Revisions

We discuss the importance of stratifying the patients according to known risk factors for delirium. It is however too complicated to make strata for all risk factors. We have chosen admittance from nursing home (a practical substitute for cognitive decline and general level of function) as our stratification variable (See also comment to referee 3, point 3A).

We do register BMI as a marker of nutrition status, line 311 (Data collection).

Sensory impairment is not routinely registered, but are taken this into account for the delirium diagnostics.

14) Hydration is, importantly, assessed but it is not clear how this is determined. Minor Essential Revisions

Hydration is assessed daily by study physician and/or on-call geriatrician. The assessment is not formalised further as this is considered a core clinical skill.

15) How will the study manage patients who require additional antipsychotic agents and how will this be handled in the analysis?

The treating physician may prescribe antipsychotics, according to standard care given by the hospital procedures. We do not interfere with these decisions and have not made new procedures for this. We register however all medications used during the stay.

Added in the manuscript (Statistical analyses, line 364): If the use of additional antipsychotics differs between treatment groups, haloperidol equivalents [11] will be included in the statistical model.

16) Major Compulsory Revisions It is prescient that the authors choose different subgroups (although their classification remains beyond operationalization), including subsyndromal delirium. Whilst reflecting a real world sample, how will this be handled in the analysis and does it affect the sample size?

The primary endpoint is the trajectory measured by MDAS. Both delirium and subsyndromal delirium will be included in these analyses, as both groups will have elevated MDAS score at inclusion and the possibility for improvement (or worsening).
Regarding the secondary endpoint of duration of delirium; this will be evaluated both to "not complete DSM-5 delirium" (but possibly still subsyndromal), and "complete delirium-free". We believe it does not forge a bigger sample size, but will increase the population base.

See also response 2A under major compulsory revision, reviewer 3.

17) Discretionary Revisions Equally, will the putative multifactorial causes of delirium be captured?

We believe our primary objective (of whether clonidine has any effect on the trajectory of delirium) must be assessed independently of the multifactorial causes of delirium. Our study is not designed to take all these different causes into consideration. But it might be relevant and interesting to do certain sub analyses. At discharge we register (in consultation with the treating physician) what is believed to be the cause(s) for the delirium in each case.

Added in manuscript (Data Collection, line 316): Possible and suggestive causes of delirium are registered in each case at discharge.

18) Discretionary Revisions Clonidine is an anxiolytic and may plausibly mediate any effect found through this role. Measurement of anxiety would therefore seem an important covariate for inclusion.

We agree that an effect of clonidine in delirium might be mediated through an anxiolytic effect. It would indeed be interesting to evaluate the degree of anxiety in these patients, but we believe that yet another measurement will increase the total amount of tests too much (for both patient and researchers). This may however be something to consider in future studies.

19) Minor Essential Revisions What is the safety profile of clonidine with respect to Lewy Body disease and if there is no data in this regard will this sub-group still be included? Minor Essential Revisions

Clonidine has been studied in patients with Alzheimer’s dementia (AD) [8, 12] and in patients with Parkinson’s disease [10, 13]. Treatment with daily doses of clonidine less than 200 mcg was well tolerated in all these patients. These studies were performed on outpatients, whereas our patients will be even closer monitored in-hospital. Thus we find it safe to include patients with Lewy Body Dementia.

We have changed the manuscript (Clinical experiences with clonidine): We omit the discussion of adolescents and add the more relevant experience with clonidine in patients with Parkinson’s disease and Alzheimer’s dementia.

See also response to reviewer 3, point 3 under “minor essential revisions”

Referee 3: Benjamin Liptzin
Reviewer’s report with point-by-point response:

Major compulsory revisions:
1A )This really should be described as a pilot or feasibility study given how complex it will be to carry out.
This is indeed a valid point of view, and given the limited knowledge on expected treatment effect, our study will, even if it should turn out to be negative, provide valuable “pilot data” for planning of a potentially larger and more definite study later. However, we have chosen to design and describe the study sufficiently rigorously, such that if positive, the results should be regarded as valid.

The first 20 patients serve some piloting purposes with respect to pharmacokinetics, as described in the manuscript, but are also included in the main study. In this way we can both

1) complete a safety review concerning the dosage and
2) still include all the valuable from these patient in the main analyses of the primary endpoint

We do not break the code (for the study physicians or other relevant personnel) and we do not perform interim analyses of the primary endpoint due to the limited sample size.

Regarding feasibility; see response to 1C.

1B) The authors do not describe how many patients are admitted to their acute geriatrics ward

   Approximately 950 admissions/year.

1C) Until doing the study they do not know how difficult it will be recruit i.e. how many patients will they have to screen to get 100 to participate. They also need to know how many patients will have or develop DSM5 delirium and subsyndromal delirium and whether they and their family will consent to participate in the study when they are admitted to the hospital for being medically ill and wanting their illness treated. They also need to know how many are admitted from a nursing home for the purposes of the stratification.

   We acknowledge these challenges. However, our experiences regarding consent from patient/family (so far in this study, and from previous delirium studies) are very positive. Very few otherwise eligible patients are “missed” due to lack of consent. If the inclusion rate is to low, we have the possibility to expand the study to other medical wards in our hospital. Stratification is carried out in order to increase the likelihood of a balanced randomisation, and for this purpose we don’t need to know the exact number admitted from nursing home.

1D) As a feasibility study the authors can also figure out the right dose of study medication to use (see uncertainty on p. 6),

   As mentioned - our safety review after the first 20 patients will answer this question.

1E) what to do with patients who don’t have informants readily available,

   See response 5 under "minor essential revisions"

1F) and whether patients will tolerate all the interviews and testing.

   The amount of interviews and testing is indeed a challenge in studies of delirium, and we have discussed this topic thoroughly. We have experience with daily monitoring for delirium, from other studies [14]. We realize that our test-battery is in the upper end of what is tolerable, but we believe it is still manageable. Our experiences so far support this.

1G) The authors acknowledge that the sample size may not be sufficient to answer the study
question of whether clonidine shortens or reduces the severity of an episode of delirium.

See our response to the editorial comment (at top).

2A) For the purposes of this initial study why include subsyndromal delirium when that may make it even more difficult to find a difference between drug and placebo? This is particularly important because your endpoints are severity and duration.

Delirium is a complex condition on a continuum (from lucid to full-scale delirium). We have sharpened the definition of subsyndromal delirium (compared to the "attenuated delirium syndrome" described in DSM5 criteria). We only include patients with a confirmed acute change in attention/consciousness and/or cognition that is not explained by other underlying condition. We have defined in our diagnostic algorithm (table 4) how we diagnose subsyndromal delirium.

We do not want to include patients where we are not sure this is a condition at the delirium axis. All patients are evaluated by one of our two study physicians (geriatricians with a special interest in delirium), and if in doubt we consult each other or an even more experienced geriatrician. We make the decision on an overall clinical assessment, leaning heavily on the tests and diagnostic algorithm described.

When it comes to measuring our primary endpoint; trajectory of delirium severity; if they have subsyndromal delirium, MDAS will not be 0, and thus they will have a possibility to get better and show this as an effect in the primary endpoint. Inclusion of geriatric patients can be a challenge due to safety exclusion criteria. We believe that including these patients will strengthen our study by allowing relevant patients being included.

Also see response reviewer 2, point 16

2B) On p. 8 you say duration will be monitored by DSM5 criteria but how will that apply to subsyndromal delirium?

Duration of delirium will be categorized as days with "full-scale delirium", days with "subsyndromal delirium" and "complete delirium-free" (lucid) days.

Also see response reviewer 2, point 16

2C) In the study design on p. 9 do you mean patients will no longer meet criteria for DSM5 criteria or no longer have any symptoms of delirium?

We mean: "No longer have any symptoms of delirium."

Patients who do not have either delirium or subsyndromal delirium (ie are delirium-free/lucid) for two consecutive days will stop taking the drug.

3A) On p. 12 why not measure cognitive decline or pre-existing diagnosis of dementia directly instead of using NH residence as a proxy?

We have considered this option. However, the pre-existing diagnosis of dementia (or lack of such) is quite often imprecise and unreliable [15] Many patients with quite severe dementia do not have a formal diagnosis in their charts. On the other hand, some people have been wrongly diagnosed with dementia due to cognitive impairment during an episode of delirium at previous admittances. Even others are diagnosed correctly per se, but at a very early stage. Further, stratification based on NH residency will not only be a
proxy for cognitive decline, but also for independence and comorbidity - other very important risk factors for delirium.

We add in the manuscript (underlined) line 276-277: “...in order to balance the groups with respect to pre-admission cognitive decline, independence and comorbidity, all important prognostic factors.”

Minor Essential Revisions
1. On p. 5 the discussion of use of clonidine could be shortened since its use in migraine or post-menopausal flushing or chronic fatigue syndrome doesn’t seem relevant to this study.

We agree and remove from the manuscript: “Other approved indications in Norway include prophylaxis against migraine (0.77 individual users/1000 inhabitants in 2012 according to the Norwegian Prescription Database) and post-menopausal flushing”

2. On p. 6 the discussion of pharmacokinetics seems excessive except as it affects dosing in this study.

We agree. We have changed/shortened this paragraph in the manuscript

3. The discussion on p. 7 of adolescents with chronic fatigue is not relevant and can be omitted. The discussion of loading doses also seems excessive.

We have changed the manuscript: We omit the discussion of adolescents and add the more relevant experience with clonidine in patients with Parkinson’s disease and Alzheimer’s dementia.

Also see response to reviewer 2, point 19.

4. On p. 8 the Safety Review is also a dose finding study. In addition to finding out what oral dose will likely be needed tolerability should be assessed, not just blood levels.

We agree. We will assess the pharmacodynamic effects (effects on heart rate and blood pressure, orthostatic hypotension and other possible adverse events). We will also assess how many doses could not be given due to hypotension, bradycardia or any other reason.

5A) On p. 10 (and p. 13) what will be done for patients who have no family or nursing home staff as informants?

In all situations we must thoroughly search for the best information available from family/close friends/nursing staff/medical records. A few patient might not be included if they have no family or other next-of-kind available.

5B) The definition of “acute change” is critical to the definition of delirium. How much change is required for a diagnosis of subsyndromal delirium? If the patient is off by one day on the date but usually knows it is that sufficient?

Just as for the diagnosis of delirium, the evaluation of how much change is required must be an overall assessment done by the physician. There is no single cut-off in the DSM-5 criteria as to the size of disturbance of cognition. The same difficulties must be met in all the patients who are recovering from delirium; at what point are they to be classified as delirium-free?
The diagnosis and measurement of severity in delirium will always to some extent be subject to an individual evaluation by the examiner. We believe it is a strength that this is based on standardised tests and carried out by a limited number of doctors.

See also response to point 2A about the diagnosis of subsyndromal delirium.

6. On p. 11, if you're using the MDAS as your measure of severity and DSM5 as your criteria for having delirium or not what's the purpose of also using the CAM daily?

This is a valid input. For all practical reasons we do not "use" the CAM daily. But with all our tests and evaluations for deciding whether DSM5 is fulfilled, it is very easy to also check/register the CAM. As the CAM is a very much used screening tool in studies of delirium, we honestly consider it highly possible that it might be asked for in a future review (publication of the results). In such a situation it would be preferable to already have this information available.

We changed (underlined) the manuscript, line 248: We will also register the Confusion Assessment Method, (CAM) daily.

7. With respect to informed consent, how "cognitively intact" can someone be and still meet criteria for delirium?

The question of informed consent in delirium research is very important. We expect most patients not to have capacity to consent at inclusion. But we believe it is important to make an individual evaluation. Some patients (eg patients without dementia who present with a fluctuating, perhaps subsyndromal delirium) may possibly have this capacity, and it is important not to wrongfully disempower these patients. The comprehensive written version of patient information is as always quite long and difficult to read. We have made a shortened and simplified version and will adapt the level of orally given information individually. We continuously evaluate whether the capacity returns during the study. We will not include any patients in this study if the close relative does not consent. We do also need their cooperation for the proxy information.

8. On p. 12 are there any restrictions on which other medications are allowed and which are not?

Yes, tricyclic antidepressants, monoamine reuptake inhibitors and cyclosporine are not allowed at inclusion, or during the active treatment with the study drug.
See Table 5 "Exclusion criteria"

9. The monitoring and safety discussion on p. 12 and the lab tests described on p. 13 seem excessive and should be justified.

As safety is a major concern in this study, we believe it is justified to discuss this more detailed and to show how we make this treatment as safe as possible for the patients.

10A) Are you aware there is a copyright on the MMSE and a royalty will need to be paid if it's used?

Thank you for pointing this out! We should have specified that we use the Norwegian version (the MMSE-NR), revised and validated in 1988 by Engedal et al. [16]

We have now specified this in the manuscript.
10B) Also on p. 13 what is the purpose of the grip strength or the data on patient distress?

Grip strength: See response 11 for referee 2.

Patient distress: We believe there is too little focus on this subject in delirium. It is not part of our primary endpoint, but might give interesting insights of a more qualitative character and inspire for more focus in this area in the future.

10C) Are the lab tests a "fishing expedition" or are there some hypotheses about sed rate, TSH or free thryoxine?

The registration of lab tests that are analysed as part of the routine at the geriatric ward is not due to any clear hypotheses. We find the effort and costs of registering these already available data very small.

10D) Was there consideration for measuring APOE subtypes?

We collect EDTA fullblood to our biobank with consents open for such analysis. We have the possibility for measuring APOE subtypes, but do not have a concrete plan at this point.

10E) The discussion about safety review on p. 14 is repetitive.

We agree and changed the manuscript accordingly.

11A) On p. 14 is the followup 1 week after the end of treatment or discharge from the hospital?

1 week after the end of treatment.

11B) At 4 months how will you handle patients lost to follow up?

We will use different conservative imputation methods for sensitivity analyses (e.g. by imputing the worst observed score of the treatment group and also by random sampling from the observed scores in the treatment group.)

Missing values will be imputed in different ways in order to explore their potential influence on the results.
A) Patients who die before the 4 months follow-up
The primary analysis will be carried out with deceased patients excluded, but we will also explore the effect of allocating the worst possible score to these patients.
B) Patients missing for other reasons than death
- The patients with complete data will be divided into four groups according to their pre-fracture IQCODE score (quartiles), and for each patient with missing data, data will be imputed from a random patient from the same pre-fracture IQCODE quartile.
- Imputation of the worst score of the primary outcome registered from any of the patients with complete data.
- Imputation of the mean score for the randomization group the patient belongs to.

11C) Will you measure persistent delirium as defined by DSM5 or include symptoms of subsyndromal delirium or change from baseline as well?

We will do a "complete" delirium diagnostic based on DSM-5 (and MDAS). In case of delirium at this time we must by medical history judge if this is persistent (as by DSM-5
"lasting weeks or months") or a new acute episode of delirium. We will also register any delirium symptoms and use the same definition of subsyndromal delirium as during the hospital stay.

Changes in manuscript line 339: We will assess the presence of persistent delirium (according to DSM-5 criteria) or subsyndromal delirium and perform the MDAS.

12A) On p. 15 how will you measure time to resolution of delirium from enrollment in the study to resolution for patients who are discharged while still delirious?

They can still be included in the primary endpoint, as it is merely dependent of all MDAS measurements available. For the secondary endpoint of length of delirium these patients will be excluded

12B) Also on p. 15 what's the estimate of how many patients will have to be screened to get an adequate sample of willing participants?

See comment 1C under major compulsory revisions.

12C) Over the 36 months how many patients will b admitted to the geriatric wards? (It would also be worth describing the types of patients admitted to these wards.)

An estimated 2850 admissions are expected to the geriatric ward in this period. The patients are usually acutely admitted, arriving directly from the emergency room/department. They are frail, geriatric patients with considerable multimorbidity and polypharmacy, with a high prevalence of infections, dehydration, acute cardiac problems, general medical problems, functional decline and delirium.

We have changed (added) the manuscript (Study population)

12D) It's also not clear what "single point in time" would be used for the MDAS.

The MDAS will be assessed daily. MDAS point 1-6 will be scored based on how the patient is during the interview. MDAS point 7-10 will be scored based on how the patient has been since the last MDAS was measured or (if it is the first evaluation or it has been > 24 hours since the last MDAS); the last 24 hours.

Literature


