Title: Modifying Delirium Using Simvastatin (MoDUS): a randomised, double blind, placebo controlled, single centre, phase II clinical trial to evaluate early administration of hydroxymethylglutaryl-CoA reductase inhibitor in the prevention and treatment of delirium in critically ill ventilated patients: study protocol for a randomized controlled trial.

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Author’s response to reviews: see over
Dear Editor

Thank you for your letter requesting to revise our paper titled “Modifying Delirium Using Simvastatin (MoDUS): a randomised, double blind, placebo controlled, single centre, phase II clinical trial to evaluate early administration of hydroxymethylglutaryl-CoA reductase inhibitor in the prevention and treatment of delirium in critically ill ventilated patients: study protocol for a randomized controlled trial.” We greatly appreciate the constructive comments and have now addressed these concerns, which we believe has considerably strengthened the paper.

On the following pages, we outline point by point responses to the comments by the Editorial Office and the reviewers. We hope our revised version will be received favourably and look forward to hearing from you in the near future.

Editorial request:

*Please include the trial registration number and date of registration at the end of the Abstract.*

The trial registration number and date of registration have been moved from the background paragraph to the end of the Abstract.

Reviewer 1

Casarin and colleagues present a manuscript describing the rationale and design for the MoDUS trial, a randomized, placebo-controlled trial that will examine the efficacy of simvastatin as a prevention and treatment for delirium in the ICU. The manuscript provides a helpful description of this potentially important trial, but a number of concerns should be addressed.
Major revisions:

1. Page 7, Clinical outcomes - Please explain the discrepancy between the duration of primary outcome assessment (14 days) and the maximum duration of treatment (28 days). It is counterintuitive that the primary outcome is not measured throughout the entire treatment period.

14 days is the primary outcome because the median length of stay in this patient group according to the Hope-ICU trial, undertaken by the same group in the same centre, is 9 IQR (5-18) (placebo group). However in the HARP trial (AJRCCM 2011; 183: 620) sustained improvements in physiological parameters were seen only after 14 days. We want to explore if longer treatment is associated with sustained and greater effect but given that the 28 day measurement is less reliable particularly post ICU when delirium screening is not being undertaken, this is less robust.

We have added in the trial conduct text section “Although the primary outcome is determined at 14 days, the study drug will be administered for up to 28 days in order explore if longer treatment is associated with sustained and greater effect but the 28 day measurement will be less reliable given an expected median ICU length of stay of nine days.”

2. Page 7, Clinical outcomes - The authors notably deviate from standard CAM-ICU usage by designating a patient with RASS -3 comatose and therefore ineligible for delirium diagnosis. First, it is unclear why they make this distinction at this point in the manuscript since the primary outcome (delirium/coma-free days) will be the same regardless of whether RASS -3 is considered coma or not. Perhaps this point should be made later (in the section mentioning incidence of delirium, which will be affected).

We agree with this comment that considering RASS -3 as coma is not relevant to the primary outcome and have moved it into the secondary outcomes section.

Second, the description provided of RASS -2 to +4 is inaccurate. Eye opening alone in response to verbal stimuli does not indicate RASS -2; eye opening with eye contact (<10 seconds) is required for RASS -2.

This point is entirely correct, we have expanded this definition to reflect the full RASS description “Patients are defined as delirious if they are awake enough to at least respond to verbal stimulation with eye opening and eye contact for less than ten seconds (RASS score of –2) and screen positive for delirium”.

Which brings me to my third point: a patient who has their eyes open (very few clinicians would consider such a patient comatose) but whose delirium makes them so inattentive that they do not make eye contact with an assessor when asked (not an uncommon scenario in the ICU) will be considered comatose rather than delirious in the MoDUS trial, an approach that is not in keeping with all the validation studies of the CAM-ICU. I am surprised that Dr. Ely, a MoDUS coinvestigator, agreed with this approach since is contradicts his teaching about use of the CAM-ICU.
The reviewer makes a valid point and at the time this protocol was being discussed Professor Ely made the same point regarding delirium being diagnosed in patients RASS-3. At Watford, however along with some other centres, we classify a patient at RASS -3 (some of whom move only) as unable to be assessed (usually due to sedation). It is acknowledged in the frequently asked questions section of www.icudelirium.org that some centres do use RASS -2 as a cutoff. We use this in day to day practice because of the clinical relevance of RASS -3 as shown by the Sedation Practice in Intensive Care Evaluation (SPICE) Study Investigators and ANZICS Clinical Trials Group who demonstrated that early deep sedation, defined as RASS -3 to -5, predicts delayed extubation and increased mortality. Co-investigators therefore agreed for the purposes of this trial (and previously Hope-ICU) that patients RASS -3 and deeper be considered to be in spectrum of coma.

We have now added into the text “For this investigation, RASS -3, (movement or eye opening to voice but no eye contact) regardless of whether disease or sedative induced, is handled as part of the spectrum of coma. Although validation studies for the CAM-ICU have demonstrated that delirium can be diagnosed in patients assessed RASS -3, at Watford along with some other centres, we routinely classify a patient at RASS -3 as unable to be assessed (usually due to sedation). We decided this because of the clinical relevance of RASS -3 as shown by the Sedation Practice in Intensive Care Evaluation (SPICE) Study Investigators and ANZICS Clinical Trials Group who have demonstrated that early deep sedation, defined as RASS -3 to -5, predicts delayed extubation and increased mortality.

3. Page 8, Biological mechanisms - Unlike the study of inflammatory markers, no rationale is provided for the study of cholinergic activity or amyloid markers, so the long list of biomarkers to be examined might be interpreted by some as a fishing expedition. A brief explanation for the inclusion of each of these markers in a statins trial would be very helpful.

We thank the reviewer for suggesting this and have added “Plasma β-amyloid measurement has emerged as a promising biomarker to identify elderly persons at risk of developing dementia. Lower β-amyloid 42 and 42/40 levels have been associated with increased risk of developing Alzheimer’s Disease. A study suggests that older adults without dementia and with lower β-amyloid 42/40 levels have an increased rate of cognitive decline over 9 years compared with those with higher levels. It may be that plasma β-amyloid 42/40 levels may be a predictor of those patients who are most at risk of developing cognitive impairment following ICU delirium. Delirium is associated not only with an unbalanced inflammatory response, but also with a dysfunctional interaction between the cholinergic and immune systems. In order to better understand the relationship between the cholinergic and immune systems in the context of anti-inflammatory interventions we will also measure biomarkers plasma acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) as indicators of cholinergic function. [27]”

Additional references:

4. Page 8, Safety - Will the trial be monitored by a DSMB? What monitoring procedures will be used?

Yes as described the Data Monitoring and Ethics committee is an independent board comprising of at least two clinicians with experience in undertaking clinical trials/caring for critically ill patients and a statistician.

For clarity we have added “The Data Monitoring and Ethics Committee (DMEC, equivalent to North American Data Safety Monitoring Board)” into the text.

With regard to the monitoring procedures, as according to the conduct of the trial, we have added “On-site monitoring visits will be undertaken by the Clinical Trials Unit and conducted in accordance with the study monitoring plan. On-site monitoring will be an ongoing activity from the time of initiation until study close-out and will comply with the principles of GCP and EU directive 2001/20/EC.

Before the study starts an initiation visit took place to ensure that all relevant essential documents and trial supplies were in place also that site staff were fully aware of the study protocol and West Hertfordshire Hospitals NHS Trust standard operating procedures (SOPs) for sponsored interventional clinical trials. During the study, on site monitoring visits will check the completeness of patient records, the accuracy of entries on CRFs, the adherence to the protocol, SOPs and GCP, and the progress of patient recruitment. Monitoring will also ensure that the study drug is being stored, dispensed and accounted for according to sponsor requirements in keeping with the principles of GCP.”

5. Page 9, Eligibility criteria - I suggest presenting the eligibility criteria earlier in the Methods section. Knowledge of the specific patient population to be studied is very helpful when considering outcomes and procedures.

Thank you for that suggestion, the eligibility criteria have been moved to immediately before the clinical outcome measures.

What is the rationale for enrolling only ventilated ICU patients? Delirium occurs at a high frequency even amongst non-ventilated ICU patients, and the proposed mechanism of benefit of simvastatin should not be limited to ventilated patients.

We agree the prevalence of delirium is high amongst ICU patients whether ventilated or not. However the Research Ethics committee needed to know that the study patient group would be a high-risk population, because most patients would lack capacity to give consent, so we restricted it to patients who receive sedatives, a patient population we know to be at the highest risk in the ICU.
How will "uncomplicated" elective surgery be defined?

We have added “planned admission, surgical procedure and recovery as predicted.”

How will you objectively identify patients "expected to be discharged within 48 hours"?

We will not be able to objectively identify patients “expected to be discharged within 48 hours”. It will be the judgement of the attending intensivist.

Provide the rationale for excluding patients recently on a statin.

We have now added in the discussion “For this study we have excluded patients prescribed statins before admission as evidence from a multi-centre randomised trial in patients with severe sepsis did not support stopping statins. Prior statin users randomised to receive placebo had higher 28 day mortality although this was not statistically significant at 90 days. In addition Morandi et al in their observational study showed that discontinuation of statins in patients was associated with increased delirium.”

6. Page 11, Sample size estimate - The authors have not provided information needed to confirm the sample size calculations. Please report both the mean and SD of delirium/coma-free days at 14 days that was used in the calculations. Also, what is the treatment effect size that can be detected (i.e., how many days is 0.5 SDs)?

Thank you, this did need clarification. We have now changed this to “Our pilot data showed a standard deviation of 4.14 in DCFDs at day 14 in a similar cohort (Shintani personal communication). Assuming this standard deviation, and assuming a type I error of 0.05 and 80% power, a sample size of 64 patients per group is adequately powered to detect a difference of approximately 2 DCFDs between the intervention and control groups, or approximately 0.5 SD. Allowing for an estimated 10% loss to follow-up, the sample size required is 142. nQuery AdvisoR version 4.0 was used for the sample size analysis (Elashoff, JD 2000).”

Lastly, why are the authors estimating 10% loss to follow-up? Since the primary outcome is measured over 14 days in an ICU population, the follow-up should be negligible. The traditional calculation of delirium/coma-free days takes into account death and discharge, so neither of these events result in loss to follow-up.

We were very conservative with regards to drop out rates. Based on previous experience, patients are lost to follow-up due to a variety of reasons, for example being transferred out to other centres where it is not possible to obtain outcome data. If drop out rates have been over-estimated, it will result in the study having additional power.

7. Page 13, Trial conduct - Will research personnel or clinical personnel be conducting CAM-ICU and RASS assessments? What kind of training will the assessors have?
The assessment is conducted by the bedside nurses who undergo regular updates in assessing patient using the CAM-ICU. We have added “CAM-ICU is a routine assessment in all ICU patients and nurses undergo regular updates and have ongoing access to advice from the ICU delirium study team.”

8. Page 15, Clinical management - The reported default sedation goal for all patients will be RASS -1. Why not RASS 0? A default goal of RASS -1 means that patients are alert and calm (RASS 0) will be given sedatives so that they become RASS -1, when evidence-based recommendations are to minimize sedation whenever possible.

The reviewer is correct and in practice our sedation goal is RASS 0 to -1 as required to enable the nurses to ensure patients comfort while requiring ventilation. We have changed that.

Does "maintained using fentanyl and propofol infusions" mean that such infusions are used (apart from the mentioned "sedation breaks") until extubation or will patients who are tolerating interruption of sedatives be allowed to continue on the ventilator without restarting sedatives (as was shown to be beneficial in the ABC Trial and was tolerated by a large proportion of patients in the trial by Strom et al.)?

Infusions of sedatives will not be restarted if the patients are tolerating interruption of sedatives. We have now clarified that in the text.

9. Page 17, Pharmacovigilance - The approach to identifying, recording, and reporting AEs and ARs is confusing, primarily because detailed definitions are not provided. Please expand this section.

We have added a table of definitions: “EU Clinical Trials Directive 2001/20 provides the definitions of adverse events and reactions used in this trial.”

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Event (AE)</td>
<td>Any untoward medical occurrence in a patient or clinical trial subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.</td>
</tr>
<tr>
<td>Adverse Reaction (AR)</td>
<td>Any untoward and unintended response to an investigational medicinal product related to any dose administered.</td>
</tr>
<tr>
<td>Unexpected Adverse Reaction (UAR)</td>
<td>An adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in the summary of product characteristics (or Investigator brochure) for that product.</td>
</tr>
</tbody>
</table>
### Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)

Respectively any adverse event, adverse reaction or unexpected adverse reaction that:

- results in death
- is life-threatening
- requires hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity
- consists of a congenital anomaly or birth defect*
- is any other important medical event(s) that carries a real, not hypothetical, risk of one of the outcomes above

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10. **Page 17, End of trial** - Will predefined stopping rules be used when the DMEC determines "whether there is any reason why recruitment should not continue"?

   The main criterion for early stopping of the trial by the TSC upon suggestions from the DMEC will be that evidence provided by the trial investigators from the trial and from other sources suggests:

   1. Proof beyond all reasonable doubt that for all, or for some types of patients, the treatment regimen is clearly indicated or contraindicated, and
   2. Evidence that might reasonably be expected to influence routine clinical practice.

   We have now included these criteria in the text.

Conducting interim analyses every 9 months is likely to result in numerous analyses; will the final p value be adjusted based on the number of interim analyses?

   We have clarified the sentence in the End of trial section as follows: The Data Monitoring and Ethics Committee will meet every 9 months to determine whether there is any reason why recruitment should not continue. Interim analyses will only be undertaken at the request of the DMEC and will only be available to the DMEC.

   Therefore the final p value will not be adjusted.

11. **Page 17, Statistical analysis plan** - Given the heavily skewed distribution of delirium/coma-free days, the t-test does not seem appropriate. Instead, the Wilcoxon rank-sum test seems a better choice. Also, will the authors use an intention-to-treat approach or will patients be allowed to cross over?

   An intention to treat approach will be used (stated). The text has been amended to include a bootstrapped t-test and Mann-Whitney test:

   The primary outcome (delirium/coma free days) is a heavily skewed distribution (bimodal with peaks at 0 and 14 days) and the groups will initially be analyzed by t-test with difference in means and 95% confidence intervals (CI) presented. A secondary analysis of these outcome measures involving a bootstrapped t-test will also be conducted to support the findings of the t-tests and confirmed using the Mann-Whitney non-parametric test.

   Minor revisions:
1. Page 4, Background - The authors make a sweeping statement regarding "commonly used pharmacologic approaches to prevent and treat delirium during critical illness" but provide only two references (one of them a survey). I suggest citing other negative trials (e.g., Girard et al. Crit Care Med 2010), acknowledging positive trials (e.g., Devlin et al. Crit Care Med 2010), and softening the tone of this sentence (e.g., "little evidence" rather than "no evidence").

We have made the changes as suggested, we have left the survey reference as information regarding commonly used pharmacologic approaches.

2. Page 5, Background - Much of the Background is better suited for the Discussion. Specifically, I would move the detailed information about why simvastatin was selected to the Discussion as well as the descriptions of studies that examined the proposed anti-inflammatory effects of statins during critical illness. The inclusion of the latter in the Background section actually distracts the reader, in my opinion, from the very important point that two large observational studies (Morandi et al. and Page et al.) support the hypothesis being tested in MoDUS (which is mentioned at the end of a long paragraph about inflammation rather than highlighted more prominently).

We have made these changes as suggested.

3. Page 5, Background - The outcome mentioned in the sentence describing the aim of MoDUS is "delirium-free days," but later in the Methods the primary outcome is delirium free-coma free days (also described delirium/coma-free days). Please use consistent terminology since delirium-free days is different from delirium/coma-free days. I suggest referring to days that are free of both delirium and coma as delirium/coma-free days (as is done on page 6 and is the phrase most often used to refer to this outcome).

We have made the changes as suggested

4. Page 11, Trial conduct - Please define "Personal Legal Representative (PerLR)" and "Professional Legal Representative (ProfLR)" since many countries do not use the same terminology.

We have included this.

5. Page 12, Trial conduct - Will a blocked randomization scheme be used?

A mixed block structure was used for the randomisation scheme.

6. Page 17, End of trial - The abbreviation DMEC is used before it is defined (in the next section).
We have corrected this error, thank you.

7. Page 25, References - Two critical references (#15 and #16) are not up to date. Both have been published in print form but are listed only as ePubs. Please updated these references.

These references have now been updated.

Reviewer 2

2. The study hypothesis is very interesting: does the prophylactic administration of simvastatin to ventilated critically ill patients increase the number of delirium-free days up to day 14 of admission, does simvastatin have an effect seen in a raft of further investigations to measure biomarkers, anticholinergic activity and beta-amyloid measured from plasma, and finally does simvastatin (short term administration) change any effects of delirium on longer term cognitive outcomes.

3. Given the possible mechanisms of action of statins in moderating inflammation against the worries about the adverse effects of statins on cognition (even knowing the jury is still out on the latter) there are certainly some very good questions to be answered here.

We greatly appreciate these comments on the importance of our study.

4 The proposed clinical outcome measures are pragmatic for a phase 2 study. The numerous biological tests seem appropriate, on the one hand there is no doubt others could be added but on other there already numerous measures increasing the possibility of a type II error – this will need to borne in mind when the results are available.

We agree with the reviewer and appreciate the study is powered for delirium/coma free days and that other secondary outcomes and biological tests will provide valuable information and signals as to potential biomarkers or mechanisms but are essentially exploratory.

5. Eligibility criteria are pragmatic. With respect to exclusion criteria, the safety aspect of high dose simvastatin treatment has been well controlled. The 80mg dose would have worried me when the study started had these measures not been put in place, although I am also more relaxed now because of the very reassuring safety data arising from the HARP-2 study.

We agree the HARP-2 study confirmed the safety aspect of the simvastatin dose used in this trial.
6 (minor revision). There is not enough information provided in the sample size calculation to determine whether the sample size has been calculated correctly or if the size of the effect being looked for is clinically relevant. It should be a simple task to add the relevant information in - the manuscript should not be published without it.

See response to reviewer 1 query regarding power calculation – query 6

7. The trial conduct description overall is very rigorous. I have only two points for clarification in a very well thought out set of trial protocols.

8 (major revision). I am aware that crushed tablets (for NG administration) have varying colour and dissolution properties when mixed with water. A line in the manuscript to assure readers that the placebo and active tablets are indistinguishable when crushed and dispersed in water for NG administration as well as when whole would be welcomed as this is important for the blinding aspect.

We appreciate this concern. A line has been included in the manuscript in the Trial conduct section as suggested.

9 (major revision). It is clear that study drug will be administered at a specific time of day (10am). It is not clear what the timing window for drawing specimens for the various biological assays is. The half-life of simvastatin is very short, approximately 2 hours though this is likely lengthened in critical illness. The pharmacodynamics of simvastatin in critical illness are even less well described. Any effect on the biomarkers studied will be consequent on the concentration of simvastatin in the target tissues and this is likely to be related to the plasma simvastatin level. Given the short half-life, it is probable that plasma simvastatin levels change from maximal concentration to near nothing over the course of a single day, and this may affect any interaction with inflammatory mediators, etc, evidenced by changes in plasma concentrations of those mediators/anticholinergic activity/beta amyloid.

This could be controlled for by doing simultaneous simvastatin levels, or by drawing blood samples for the biomarker studies within a reasonable time window in relation to when the dose is administered, e.g. 3-6 hours post dose. There may of course be pharmacokinetic or pharmacodynamic data from other studies that indicates this is not necessary, and if this is so, this should be cited.

We thank the reviewer for suggesting to measure the simvastatin levels when testing the biomarkers levels. We have looked into this but currently we do not have funding to measure simvastatin levels. We will continue to look into this as an option and are in contact with the study team who undertook HARP-2 who are planning to measure simvastatin levels.

10 (discretionary revision). The overall statistical plan seems fine though it has not yet been fully developed. A 5% significance level is reasonable given the small scale nature of this study, although a Bonferroni correction may be required. The health economic analysis is standard, and fairly ambitious for a 164 patient study.
Response:  *Text amended to mention multiple testing:*
*All analyses will be conducted at the 5% level of significance unless adjustment for multiple testing is needed.*
*The health economic analysis is based on recommendations for a study of this kind, we agree the conclusions will be limited.*

11. I really like the inclusion of ICUsteps (patients) on the trials steering committee.

*We thank the reviewer for this comment.*

12 (discretionary revision). The discussion section is not particularly long, but does the job. I would take out the word “brain” in the final paragraph of the discussion. Statins may very well have an effect on inflammatory pathways in the brain itself, but this study looking at peripheral levels of biological mediators would not be able to say one way or the other.

*We have revised the discussion in line with the other reviewers comments. We have taken the word brain out where suggested.*