Reviewer’s report

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

Version: 1 Date: 22 August 2014

Reviewer: Eamonn Eeles

Reviewer’s report:

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.

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

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

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

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 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

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

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

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

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

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

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

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 Hydration is, importantly, assessed but it is not clear how this is determined. Minor Essential Revisions How will the study manage patients who require additional antipsychotic agents and how will this be handled in the analysis?

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?

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

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. 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