Reviewer's report

Title: Rationale and design of the randomised clinical trial comparing early medication change (EMC) strategy with treatment as usual (TAU) in patients with Major Depressive Disorder - the EMC trial

Version: 1 Date: 27 January 2010

Reviewer: Allan House

Reviewer's report:

1. The submitted protocol is generally clear and well written. However, is would benefit from clarification in a number of areas:

   a) The trial participants are described as hospitalised at recruitment. Does this mean inpatient? In the UK that would mean only the most severely ill. Or outpatient? Care systems for depression vary greatly across Europe and expansion in the description of pathways to care and case mix in the trial will aid interpretation.

   b) The randomisation is not stratified by severity of symptoms (or duration). Given the influence of severity on AD response this decision should be explained.

   c) It appears from my reading (is this correct) that adverse events and severe adverse events will not be sought by routine standardised inquiry – only that those identified by study psychiatrists will be recorded on a standardised format. There is no mention of recording of episodes of self harm, attempted or completed suicide.

   d) The section on analysis of primary endpoint (top P.14) is unclear. Will missing data in the ITT be replaced with LRCF? And how will classifying patients with all missing data as non-responders be dealt with if the researchers are wrong and data are not missing at random? Why are other more rigorous approaches to missing data, such as multiple imputation, not being considered?

2. The discussion is largely taken up with a repetition of the points made in the background. I would have liked to see some consideration of a number of design issues.

   a) The advantages and disadvantages of other designs, such as randomising all participants to TAU programme v programme where EMC is a protocol option rather than only randomising early non-responders.

   b) The disadvantage of primary outcome being at only 56 days given what we know about the later course of depression.

   c) The absence of an integrated economic analysis, especially given claims made in the protocol for the economic importance of the findings from the trial.