Reviewer’s report

Title: Role of cerebral hypoperfusion in multiple sclerosis (ROCHIMS): study protocol for a proof-of-concept randomized controlled trial with bosentan.

Version: 0 Date: 09 Oct 2018

Reviewer: Monica Busse

Reviewer’s report:

This study protocol describes a randomised controlled trial of bosentan, dual endothelin receptor antagonist used in the treatment of pulmonary artery hypertension, compared to placebo with the primary outcome of change in NAA/creatine ratios (reflecting changes in axonal mitochondrial metabolism. The authors expect an increase in cerebral blood flow after treatment with bosentan. The trial is registered on the EU clinical trials register.

The background and rationale for the trial is well articulated and the concept is of interest. The mechanistic evaluations that are proposed appear to be robust and well described. There are however important areas in relation to the protocol description which need to be addressed in line with SPRIT statement.

Randomisation is conducted using an online research randomiser. There is no information in balancing variables that may be relevant in the randomisation process. There is no information on methods for allocation concealment or maintenance of blinding. There is no information on data management including safety reporting. The sample size calculation is difficult to understand. This is a proof of concept study rather than an efficacy study yet the calculation refers to a significant treatment effect. The follow up period is 1 month. It would be helpful to justify this length of follow up in relation to the clinical measures. Surely fatigue, and cognition would require longer follow up periods? The study flow chart is unclear (it would be helpful to provide a Schedule as recommended in SPIRIT).

Perhaps this should be written up as a mechanistic evaluation with the clinical outcomes being more relevant if the mechanistic changes that are expected are truly shown.

Level of interest
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