Reviewer’s report

Title: Effect of Eicosapentaenoic acid/Docosahexaenoic acid on Coronary High-intensity Plaques Detected with Non-contrast T1-Weighted Imaging (The AQUAMARINE EPA/DHA Study): study protocol for a randomized controlled trial

Version: 0 Date: 31 Jul 2017

Reviewer: Marion Mafham

Reviewer's report:

I have a number of concerns about this manuscript which largely related to the trial design rather than the manuscript itself.

1. Aims of the study: The authors mention the JELIS trial (reference 17) as evidence of a beneficial effect of supplementation with omega-3 fatty acids on the risk of major vascular events. However, they ignore a large number of studies indicating no effect of omega-3 fatty acid supplementation on vascular events [Wen YT, Dai JH, Gao Q. Effects of Omega-3 fatty acid on major cardiovascular events and mortality in patients with coronary heart disease: a meta-analysis of randomized controlled trials. Nutr Metab Cardiovasc Dis. 2014 May;24(5):470-5]. Against a background of several negative cardiovascular outcome trials it is difficult to see how this trial of 150 people assessing an imaging measure is going to change practice. Furthermore there are a number of large on-going trials assessing omega-3 fatty acid supplementation which are not mentioned, such as the VITAL study and the ASCEND trial which together include over 30,000 people randomized to 1 gram of omega-3 fatty acid supplement or placebo. There remains the possibility that the higher doses of omega-3 fatty acids planned in this study might have additional effects but that argument needs to be made explicitly.

2. Sample size: The sample size calculation looks optimistic. The suggestion is that fewer than 4 out of 50 people in each group will drop out. There is no plan for a run-in period so the number of drop outs might be larger than this.

3. Blinding: Why not have a placebo controlled study? If a blinded study is not possible then at least those grading the images need to be blinded. This is not discussed.

4. Assessments: Is it really necessary to do both cardiac MR and coronary angiography? This seems to be exposing people to unnecessary radiation when the cardiac MR is the main outcome.

5. Recruitment: How many people with CAD have High Intensity Plaques? How many people will need to be screened with cardiac MR to find a potentially eligible individual with this lesion?
6. Study organisation: How will this study be organised? Who is the sponsor? Is it registered with a trials registry? How many centres will be involved?

7. Exclusion criteria: Why are individuals with higher LDL-cholesterol or diabetes plus HbA1c over 8% excluded? It might be quite hard to find individuals with the High Intensity Plaque and strict exclusion criteria might make it even more difficult to recruit. How is "clinically significant renal impairment defined"?

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