Reviewer's report

**Title:** New therapeutic approach to Fragile X syndrome based on a randomized placebo-controlled double-blind phase II pilot trial to test the effectiveness and safety of a combination of Ascorbic acid and Alpha-tocopherol.

**Version:** 1  
**Date:** 14 April 2014

**Reviewer:** Maija Castren

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De Diego-Otero et al. present a study protocol to test the effects of ascorbic acid and alpha-tocopherol on behavioral phenotype, cognitive skills, family and scholar life, and oxidative stress parameters in blood of individuals with fragile X syndrome (FXS) when compared with controls without treated. The study is based on the findings in FXS mice, which have provided evidence that oxidative stress associates with FXS and that the antioxidants may be beneficial in FXS. The study design includes male patients at the age of 8-16 years. The sample size was established by means of a pilot scheme based on a phase II effectiveness trial, with 30 patients monitored over 6 months. The examinations are planned 12 weeks (3 mo; t1) and 24 weeks (6 mo; t2). There are some concerns in the study to be answered before publication of data:

1. Since the examinations will be performed in short interval, how the learning effects in tests will be avoided?
2. Does alpha-tocopherol accumulate in the body?
3. There are many trials of individuals with fragile X syndrome on-going and they should be introduced based on the action of drugs used in the trial in Discussion.
4. There are some special concerns in Introduction:
   - Martin and Bell described the first families which clearly demonstrated the X-linked inheritance of mental retardation caused by Fragile X syndrome. It should be noticed that although some female individual showed intellectual disability it was milder than in males and the boys with severe intellectual disability were born to normally intelligent mothers.
   - Reference #9 is incorrect. References #7 and 8 should be together.
   - The neuropathological findings should be based on references from human studies (references #10-13 are all mouse studies).
   - References #20 and 21 should be replaced by a review or up-dated references describing better the properties of FMRP as a RNA binding protein.
   - GSH is introduced with an abbreviation many times.
   - Reference #81 is primarily for alpha-linolenic acid supplementation and not for vitamin C.

Discretionary Revisions:
- What are the urine and blood tests to be performed?

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests.