Author's response to reviews

Title: The effect of homocysteine-lowering with B-vitamins on osteoporotic fractures in patients with cerebrovascular disease: substudy of VITATOPS, a randomised placebo-controlled trial

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Author's response to reviews: see over
Further to the original cover letter submitted (below) and subsequent email correspondence with Emily Crow, Executive Editor, I resubmit our paper. As agreed the changes are:

1. Re CONSORT requirements: the first sentence in first paragraph of methods now states (*addition in bold/italics*) - “The rationale, methods, CONSORT flowchart and primary results of the VITATOPS trial have been published [22, 23].”

2. Re names of the specific ethics committees: the second paragraph of methods now states (*changes and new information in bold/italics*) - The study was conducted in accordance with principles of good clinical practice and the Declaration of Helsinki, and received ethics approval in the United Kingdom from the Multicentre Research Ethics Committee for Scotland A, in New Zealand from the Multi-region Ethics Committee and from local research ethics committees applicable to each participating centre. A full list of the 127 participating centres is available in an additional file [see Additional file 1].

Please note that both the UK and NZ approving ethics committees have changed their names since the study was initiated and we have provided the names of the committees applicable at the time the study was conducted.

Thank you for your further consideration

Dr John Gommans FRACP

14 January 2013

The effect of homocysteine-lowering with B-vitamins on osteoporotic fractures in patients with cerebrovascular disease: substudy of VITATOPS, a randomised placebo-controlled trial.

As corresponding author I submit this report of a “RESEARCH TRIAL”; a randomised placebo-controlled double blind clinical trial (RCT) - a substudy of the VITATOPS trial, on behalf of my co-authors.
Summary of Study Findings: Despite theoretical and some study evidence for potential benefit of B-vitamin therapy on fractures outcomes, the VITATOPS study showed that once daily therapy with folic acid, vitamin B₆ and vitamin B₁₂ for a median of 2.8 years in 8,164 patients with recent stroke or TIA had no significant effect during a median 3.4 years follow-up on their overall incidence of osteoporotic fractures. A modest effect of B-vitamin therapy was not excluded due to the low numbers of fracture outcome events in this population. Whilst awaiting the results of other prospective randomised controlled studies (B-PROOF) our data suggests no adverse or favourable effect of homocysteine-lowering with B-vitamins on fracture outcomes.

Why BMC Geriatrics: The target audience of BMC Geriatrics includes clinicians interested in aged-related problems such as stroke, osteoporosis and fractures that are the focus of our paper, and the journal has already published the methodology of B-PROOF, a similar but still ongoing study of B-vitamins for fracture prevention whose results are awaited.

To the best of our knowledge, our paper is only the third RCT to report anywhere on this topic, and the first to span multiple countries. The other two studies (HOPE-2 and the Sato study of disabled Japanese stroke survivors) gave conflicting results. Therefore this paper is of interest to your readers and researchers, and will inform ongoing (eg B-PROOF) and future research.

Although our paper was underpowered due to the low rate of fracture outcome events it adds to the volume of relevant data from the other two published studies and its publication will assist with any meta-analysis, especially when the B-PROOF study results are released. Our paper discusses the likely reasons for the low fracture rate in our study population.

We confirm that this study (initiated in November 1998 with final follow up in June 2009) conformed to the original pre-specified analysis plan and its subsequent amendment in 2004 to specifically include osteoporotic fractures as a prospectively reported secondary outcome event. Our discussion addresses the potential issues relating of those patients recruited before 2004, especially the 425 participants (5%) who left the study prior to the prospective reporting of all fractures in 2004.

Reviewers: We have no objections to any specific reviewers.

We suggest as potential reviewers Prof Ian Reid of Auckland University, New Zealand email: i.reid@auckland.ac.nz as he is aware of our research but had no actual involvement in the study. Alternatively Prof Ian Cameron, who is also a section editor for BMC Geriatrics, (Sydney University email: ian.cameron@sydney.edu.au) is also aware of our work.

Thank you for your consideration
Dr John Gommans FRACP

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