PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The effect on quality of life of Vitamin D administration for advanced cancer treatment (VIDAFACT study). Protocol of a randomized controlled trial
AUTHORS	Martinez-Alonso, Montserrat; Dusso, Adriana; Ariza Carrió, Gemma; Nabal Vicuña, Maria

VERSION 1 - REVIEW

REVIEWER	Ayako Matsuda Teikyo University School of Medicine Japan
REVIEW RETURNED	04-Aug-2014

GENERAL COMMENTS	Thank you for asking me to review the manuscript. Herewith I am giving my comments. Hope these comments will be helpful for the authors. *The authors described that a randomized triple-blind placebo-controlled multicenter trial has been designed in Summary, while a randomized double-blind phase II/III placebo-controlled multicenter trial has been designed in Methods and analysis. Which is correct? *The authors will assess using some questionnaires (EORTC QLQ-C15-PAL, FACT-F, EQ-5D). The authors should indicate the references about each questionnaire. *In Sample size, the authors described that this study was designed to detect differences of 15% or more in the proportion of patients with improved HRQoL between the groups. What is the evidence about that? *In Statistical analysis, what is the evidence about response rates of 30%?

REVIEWER	Cedric F. Garland Univ of Caloif San D iegio Dept Family &Y Prev Medicine
REVIEW RETURNED	03-Nov-2014

GENERAL COMMENTS	This is a report of an important clinical trial. It is very worthwhile to get the design of this study and supporting literature to the biomedical community. I suggest adding a few citations in support of benefits of vitamin D3 against cancer. This will provide reassurance

	that no harm will be done. If I were doing this study, I would use 40,000 IU/day of vitamin D3. These patients are seriously ill, and the very minor risks associated with intake of 40,000 IU/day can be minimized by periodically checking 25(OH)D and serum calcium concentration, dropping anyone whose serum calcium is persistently > 11.9 mg/dl or whose serum 25(OH)D is persistently > 150 ng/ml. The authors should cite these papers pertinent to vitamin D and its safety re cancer: 1. Garland CF and Garland FC. Int J Epidemiol 1980. 2. Garland CF1, Garland FC, Gorham ED, Lipkin M, Newmark H, Mohr SB,F.Meta-analysis of vitamin D sufficiency for improving survival of patients with breast cancer. Anticancer Res. 2014;34(3):1163-6. 3.Garland CF1, Garland FC, Gorham ED, Lipkin M, Newmark H, Mohr SB, Holick MF. The role of vitamin D in cancer prevention. Am J Public Health. 2006 Feb;96(2):252-61. This is an excellent study design. If I were doing this study I would give the test group patients 40,000 IU/day of vitamin D3 rather than 4,000 IU/day, to maximize cnace of results iun 42 days. I would also extend the study to a duration of no less than 1 year., preferably 3 years or as long as each patient survives, with periodic testing of 25(OH)D and serum calcium. I would exclude anyone with hypercalcemia (> 10.5 mg/dl) at enrollment. This is very important work that is very likely to benefit millions of people who suffer from terminal cancer. Bravo to you on proposing this fine research.

VERSION 1 – AUTHOR RESPONSE

Reviewer Name Ayako Matsuda
Institution and Country Teikyo University School of Medicine
Japan
Please state any competing interests or state ‘None declared’: None declared

Thank you for asking me to review the manuscript.
Herewith I am giving my comments. Hope these comments will be helpful for the authors.

*The authors described that a randomized triple-blind placebo-controlled multicenter trial has been designed in Summary, while a randomized double-blind phase II/III placebo-controlled multicenter trial has been designed in
Methods and analysis.
Which is correct?

The correct one is triple-blind, since the statistician analyzing the outcomes is also blinded to the assigned intervention. We used “double-blind” since this is pre-specified in the EudraCT registry. The 2010 CONSORT Statement specifies that authors and editors should not use the terms "single-blind," "double-blind," and "triple-blind" and instead specify who was blinded after assignment to interventions, but the fact is that these terms are still used. We have changed the design description to “a randomized triple-blind phase II/III placebo-controlled multicenter trial” in both paragraphs.

*The authors will assess using some questionnaires (EORTC QLQ-C15-PAL, FACT-F, EQ-5D).
The authors should indicate the references about each questionnaire.

These references have been added.

*In Sample size, the authors described that this study was designed to detect differences of 15% or more in the proportion of patients with improved HRQoL between the groups.
What is the evidence about that?

The research team considered that a 15% difference was clinically relevant. Differences below 15%, will not suffice to demonstrate the clinical significance of the effect of supplementation with vitamin D on quality of life.

*In Statistical analysis, what is the evidence about response rates of 30%?

This 30% is the double of the expected minimum difference between the study groups (15%) that was used to estimate the sample size. We planned the second interim analysis with a stopping rule so that if the improvement difference is 30% or greater, all the participants could benefit.

Reviewer Name Cedric F. Garland
Institution and Country Univ of Caloif San D iegio Dept Family &Y Prev Medicine
La Jolla CA 92093 USA
Please state any competing interests or state 'None declared': None declared

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Doses of 40,000 IU daily will not be accepted by our Ethical Committee for human studies, as they are not allowed even for normal individuals. It could be possible to use doses higher than 4,000 IU/day of vitamin D to quickly correct vitamin D deficiency, but the safety of such doses is not tested and in patients with advanced cancer under palliative care, considering their weakness and poor general health status, might be counterproductive. The goal of our study is to demonstrate whether our patients would benefit or not of receiving the Tolerable Upper Intake Levels of vitamin D for adults, which is established at 100 mcg (4000 IU) per day by the European Food Healthy Authority. This dosage may not be enough to detect the effect of supplementing with vitamin D during 28 days, but the conservative approach was chosen to expedite the initiation of the study.

We completely agree with less conservative approaches in a near future. This is only the beginning of a step by step research Unfortunately, the life expectancy of patients with advanced cancer in palliative care is often no longer than a year. In our opinion, the valuable interventions for these

patients are those which will offer an improvement in quality of life improvement life shortly after the initiation of the therapeutic strategy. For this reason, the intervention has a duration of only four weeks. Our patients are frail and often unable to attend the outpatients clinic or unwilling to do blood tests.

Due to the clinical complications that patients with hypercalcemia suffer, we assumed that these patients would not be included due to the remaining exclusion criteria, but we agree with the reviewer that it is better to specify it among the exclusion criteria.