Reviewer's report

Title: Vitamin D supplementation in the management of knee osteoarthritis: study protocol for a randomized controlled trial

Version: 2 Date: 17 May 2012

Reviewer: Kent Johnson

Reviewer's report:

This is a very well done report. The rationale for an RCT and its design are clearly articulated. I have the following comments/suggestions.

Sample size:
Could you discuss this more fully and be more transparent, and, in particular, (i) give the standard deviation used in the calculation and its source, (ii) relate your 2.2% medial tibial cartilage volume loss to your previous findings (A&R 2009;60:1381) of a 2.1% volume loss in vitamin D sufficient patients and 2.9% in Vitamin D insufficient patients, and (iii) relate your findings to those of Losina (Abstract 385, Osteoarthritis and Cartilage 19S1, 2011, page S177) of a medial femorotibial compartment cartilage volume loss of 6.7% over 2 years?

Analysis plan:
Could you unambiguously specify the primary analysis: linear regression, logistic regression, covariates, adjustments, method of dealing with missing data, etc.?
Consider a secondary analysis of cartilage volume using a binary measure based on MCID where “success” is “progression less than cartilage volume MCID” and “failure” is “progression more than the cartilage volume MCID”.

Overall interpretation:
I assume the safety profile of vitamin D will not be problematic. Nevertheless, a statistically significant but quantitatively modest lessening of cartilage volume loss will be difficult for clinicians to interpret unless the WOMAC result is strongly positive. If volume loss is only modest and there is no dramatic WOMAC gain, is long term treatment with an uncertain benefit worthwhile? The point here is that cartilage volume loss has not been established as a valid surrogate for, i.e., predictive for, say, progression to joint replacement, and past reliance on observational data alone to support surrogacy has often led to erroneous conclusions. Interventional studies targeting both the putative surrogate marker, volume loss, and some patient important clinical outcome are needed to establish valid surrogacy.
In light of this, consider making cartilage volume and the WOMAC co-primary endpoints, and pre-specify that a successful trial needs success in both co-primary endpoints. At a minimum, assuming the trial is well underway but no patient is yet finished two years, you might add an exit (2-year) semi-flexed knee
x-ray to enable the dataset to be studied along with others that have measured X-ray change over two years.

In the same vein, the language in the summary paragraph seems overstated. In particular, the sentence: “If correcting vitamin D deficiency can reduce rates of cartilage loss to lower levels as seen in older people without OA, it will significantly prolong the time it takes to reach end-stage OS eventually requiring joint replacement.” This is only true if cartilage volume slowing associated with a therapy predicts a reduction in time to or number of joint replacements associated with therapy, a claim to date not substantiated.

One minor suggestion:
P10/Cartilage column: The second sentence regarding resampling should be explained in language that does not require the reader to dig back into multiple past reports to have some understanding of what you’re doing.