LETTER

Reply to Grey and Bolland: Findings of prespecified per-protocol analysis are valid

We thank Grey et al. for their comments (1). However, contrary to their assertion, our article did not contend that our results provide evidence for treatment efficacy of adjunctive vitamin D in tuberculosis treatment (2). Our finding that sputum smear conversion was accelerated in patients in the per-protocol population who received adjunctive vitamin D is not a "claim" but an observation. We reported it because it places the immunological findings of our study into context. It might well be supposed that suppression of IFN-γ, TNF, and IL-12—so central to the protective immune response to *Mycobacterium tuberculosis* (3)—would be associated with impaired treatment efficacy. The effect of the intervention on sputum clearance that we observed is therefore worthy of note. The relevance of the negative result of the trial by Wejse et al. (4) is limited, given that the intervention did not influence participants' vitamin D status in that study (5).

We are well aware that caution should be applied in the interpretation of analyses conducted in per-protocol trial populations. However, such analyses have their place, as acknowledged in the latest Consolidated Standards of Reporting Trials (CONSORT) guidelines, which dropped the specific requirement for results of intention-to-treat analysis to be reported in favor of a clear description of exactly who was included in each analysis (6). Such a description is provided in our report (2). The utility of per-protocol analyses in clinical trials is that they reduce "noise" and enhance the ability to detect and characterize "signal." In designing this immunological substudy, we assumed that the signal (immunomodulatory effects of micronutrient supplementation) would likely be subtle and the noise (effects of antimicrobial therapy on immune responses) substantial. It seemed rational, therefore, to focus our investigations on a protocol-compliant population, and for this reason we prespecified this analysis in our trial protocol. This approach did not "violate the randomization": baseline characteristics of patients in intervention vs. control arms of the per-protocol population in our study were comparable (2). We appreciate that results of per-protocol analyses may have reduced generalizability, and for this reason our article fell well short of claiming that our results justified a change in clinical practice. We therefore stand by the conclusions of our report: namely, that if the immunomodulatory effects of vitamin D supplementation can be augmented—by administering vitamin D at higher doses, for example—then tuberculosis patients might derive a clinical benefit from this intervention.

Adrian R. Martineau*[1]*, on behalf of the AdjuVIT trial investigators
Centre for Primary Care and Public Health, Blizard Institute, Queen Mary University of London, Barts and the London School of Medicine and Dentistry, London E1 2AB, United Kingdom

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The author declares no conflict of interest.

[1]E-mail: a.martineau@qmul.ac.uk.