

### Dr Khin and Colleagues Reply

**To the Editor:** We acknowledge the potential contribution of “professional patients” to the rising placebo response, declining treatment effect over time, and persistently high failure rate seen in placebo-controlled major depressive disorder (MDD) trials.<sup>1</sup> Unfortunately, there are no systematic data to document the impact that such subjects might have. The US Food and Drug Administration (FDA) has little capacity to investigate this concern, because patients are deidentified in the data submitted as part of new drug applications. Even site inspections by FDA’s Division of Scientific Investigations do not provide an opportunity to address this potential problem, because these typically focus on only a few sites selected from multicenter trials. FDA Center for Drug Evaluation and Research clinical investigator inspectional databases<sup>2</sup> (eg, subjects receiving simultaneous investigational drugs as the deficiency code) have so many limitations that these also would not be a particularly useful source for a comprehensive look at this issue.

Trying to assess patient compliance with taking the assigned treatment is useful independent of the concern about “professional patients,” so we agree with Dr Shiovitz and colleagues regarding the suggestion of collecting pharmacokinetic samples during these trials. The FDA has in fact encouraged sponsors to include pharmacokinetic measurements in the design of these trials. It is unclear, however, that such assessments would help in definitively identifying “professional patients,” because even legitimate patients may sometimes fail to take assigned treatment.

The suggestion of groups independent of the FDA setting up central databases for tracking participation of professional patients

in clinical trials is worthy of consideration. Close attention is needed, however, to a variety of factors in the construction of this type of individual patient-level database, including, importantly, legal issues on patient privacy<sup>3,4</sup> and human subject protection.<sup>5</sup> These considerations become increasingly important as globalization of clinical trials continues to increase.

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