

## Failure Rate and “Professional Subjects” in Clinical Trials of Major Depressive Disorder

**To the Editor:** We commend Khin et al<sup>1</sup> on a thorough and comprehensive article detailing the declining treatment effect and high failure rate in major depressive disorder (MDD) trials. We wish to highlight an area that we believe is a major factor in the increasing failure rate of studies: the choice of subjects. Specifically, we believe that failure rates are rising due to the increase in “professional subjects,” who go from site to site, learning inclusion and exclusion criteria and collecting stipends. Professional subjects are assisted in this by several Web sites.<sup>2–4</sup>

The changing nature of our subjects as an explanation for the declining treatment effect in central nervous system (CNS) studies has received only minimal attention.<sup>5</sup>

Factors that may facilitate the effect of professional subjects are many: investigators are loath to “blame the patient” or admit they cannot always detect professional subjects. Pharmaceutical companies and contract research organizations are under time pressures to enroll studies, do not appropriately compensate for prescreening, and have not shared their internal data on duplicate subjects.

In speaking with individual sponsors (who wish to remain anonymous), we were told that the number of duplicate subjects *within* a protocol is often >5% of screened subjects. If this statistic were tracked *between* sponsors, this number would certainly be higher.

The following brief examples may help to highlight the issue.

**Example 1.** Subject A had just completed visit 8 in a treatment-resistant MDD study. The site was notified by the sponsor that his initials and date of birth were a match to identifiers captured on visit 1 lab reports at 2 other sites participating in the same protocol.

**Example 2.** A clinical research coordinator who had worked until 6 months ago at a site specializing in early drug development told her new principal investigator that the depressed subject B reading consent for an MDD study in Room 2 had been in at least 1 inpatient schizophrenia study of an investigational antipsychotic at her previous site less than a year ago.

**Example 3.** A psychiatrist and his spouse work together as investigator and rater at a site doing a repetitive transcranial magnetic resonance imaging (rTMS) study. The rater works separately at a second CNS site about a mile away. She arrived at the second site in the afternoon to find subject C, whom she had just rated that morning at the rTMS site, in the waiting room filling out paperwork. “I didn’t know you’d be here too,” the subject laughed.

**Example 4.** Subject D was enrolled in a placebo-controlled study of recurrent MDD. Her total Montgomery-Asberg Depression Rating Scale score was 31 at baseline, but improved to a score of 2 at the end of the study. When the blind was broken, it was revealed that subject D was on placebo. Later, it was discovered that she had previously participated in an anxiety study using a slightly different name and had denied any history of depression.

Raising entrance criteria, while better for the overall outcome of many trials, may allow professional subjects who can report high levels of pathology to have a greater proportional negative effect on study outcome.<sup>1</sup>

Subject dishonesty in clinical trials, while not new, seems to be on the rise. We contend that this may be due to social changes that have made cheating more acceptable, the downturn in the economy, stipends for study participation, and the rise of the Internet.<sup>6</sup>

Investigators and sponsors could greatly benefit from knowing when a subject last participated in a study and for what indication. In addition, frequent pharmacokinetic samples would help characterize noncompliant subjects.

Investigators have not worsened over time, suddenly diagnosing and rating poorly; with training, they have become better than ever. It is time to acknowledge that our *subject* pool has changed—to the detriment of CNS drug development.

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doi:10.4088/JCP.11lr07229

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