Dr. Freedman:

I am one of four psychologists that have closely analyzed STAR*D's published results and are submitting our manuscript, "***The Current Status of Antidepressants' Efficacy and Effectiveness Research*"** to the American Journal of Psychiatry (AJP) for publication. While reading through the eight journal articles presenting STAR*D's findings—six of whom were published in AJP—we found indications of researcher bias inflating antidepressants' published remission rates while minimizing relapse rates during continuing-care.

We then investigated further by reviewing STAR*D's Clinical Procedures Manual and articles by STAR*D's authors describing its background, rationale, and research design. Through this investigation, we discovered proof that after data collection STAR*D's researchers changed their pre-specified outcome measures, study inclusion criteria, and means of analysis. These post-hoc changes inflated the reported number of treatment remissions as well as minimized the reported relapse rate.

Recent meta-analyses of efficacy trials submitted to the FDA have found that researcher bias often occurs in industry-funded research when the researchers fail to report in journal publications the negative results for their pre-specified primary outcome measure as submitted to the FDA and instead highlight positive results from a new measure as though it was their primary measure of interest. This is one of the biasing behaviors that occurred in STAR*D.

In contrast to STAR*D's report of positive findings, our analysis found antidepressants to be far less effective than previously realized. Only 108 of STAR*D's 4,041 patients (2.7%) who were initially started on citalopram in step-1 had an acute-care remission (after up to four treatment trials) and during continuing-care neither dropped out nor relapsed—once again scoring in depression's moderate to more severe range. The accuracy of this analysis was confirmed in several email exchanges that I had with Dr. Stephen Wisniewski, STAR*D's chief biostatistician. It is unclear how many of these 108 patients had only mild depressive symptoms when first started on citalopram in step-1 (due to changes in study inclusion criteria), nor how many actually remained "*in remission*" during continuing-care.

While disclosures of researcher bias in industry-funded research have become more common, our analysis documents such behavior in a 35-million dollar taxpayer-funded study that is by far the largest and most important antidepressant effectiveness study ever conducted.

Whereas there are numerous instances of bias in STAR*D's presentation and interpretation of its results, our paper focuses on those which are most critical to the furtherance of depression's evidenced-based treatment. The manuscript first reviews recent meta-analyses of efficacy trials submitted to the FDA. It then analyzes STAR*D's findings using the pre-specified research outcome measures and analytic procedures wherever possible.

As designed, the Hamilton Rating Scale for Depression (HRSD) was STAR*D's pre-specified primary outcome measure and the Inventory of Depressive Symptomatology—Clinician-Rated (IDS-C30) the secondary one for identifying remitted and responder patients.

Our review found that after data collection, STAR*D dropped the IDS-C30 never reporting the remission and response rates for this pre-specified measure. STAR*D replaced it with a version of the Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR) that explicitly was not designed for use as a research outcome measure but rather as a clinical management tool to guide treatment. In the six steps 1-4 articles, the QIDS-SR was the secondary measure for identifying remissions and sole measure for identifying responders while the HRSD was the primary measure for identifying remitted patients. In its AJP summary article, STAR*D dropped the HRSD and only used the QIDS-SR to report step-by-step remission rates.

This change alone substantially inflated STAR*D's reported remission rate. STAR*D then built on its inflated QIDS-SR remissions to calculate a 67% "*cumulative*" rate after up to four medication trials. STAR*D acknowledged that this assertion assumed no dropouts and the same remission rate for persisting patients as those who exited. These assumptions though are not true in the real-world and were certainly not true in STAR*D since as our analysis documents more patients discontinued treatment in each step than had a remission

By recommending continuing-care for all patients who achieved a remission, STAR*D also provided a naturalistic test of APA's continuation-phase guideline that "*following remission, patients who have been treated with antidepressant medications in the acute phase should be maintained on these agents to prevent relapse.*" This guideline received the expert panel's highest clinical confidence rating.

However, as our analysis shows, of the 1,518 remitted patients who consented to STAR*D's free exemplary continuing-care, only 108 (7.1%) survived it without relapsing and/or discontinuing treatment. STAR*D's 7.1% survival rate for once remitted patients, calls into question APA's continuation-phase guideline. STAR*D's acute and continuing-care findings when accurately presented make a strong case for a thorough reassessment APA's current guidelines for treating depression.

Given that we are psychologists reviewing the current status of antidepressants' efficacy and effectiveness research, we request blind review to ensure that professional-guild bias does not affect the objectivity of AJP's peer-review process. In that our review documents evidence of researcher bias that likely should have been identified in STAR*D's prior AJP articles, we also request that the associate editors and peer-reviewers involved in those publications not be included in our manuscript's review.

STAR*D's two most important pieces of data are that 4,041 patients were started on citalopram and there were only 108 patients (2.7%) who had an acute-care remission after

up to three subsequent treatments and during continuing-care did not dropout and/or relapse. This data is not disclosed in any AJP publication and required extensive investigation and two email exchanges to uncover. On request, I will forward these emails to you so that you can verify them with Dr. Wisniewski and confirm their verification to the peer reviewers.

Per AJP's request, the following are six peer reviewers whom we believe can objectively evaluate our manuscript's merits:

- John S. McIntyre, M.D., chairman of APA's guideline steering committee
- Craig Nelson, M.D., author of the AJP editorial that accompanied STAR*D's summary article who correctly observed (and AJP rightly highlighted) *"In my opinion, the authors have cited the positive side of the coin here."*
- Steven Sharfstein, M.D., past-president APA
- Donald Klein, M.D., professor emeritus at Columbia
- Erick Turner, M.D., professor at Oregon Health and Science University
- Joseph Glenmullen, M.D. professor at Harvard and author of "Prozac Backlash"

My fellow authors and I look forward to a prompt and objective review,

H. Edmund Pigott, Ph.D.