Introduction to the STAR*D Special Section

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This issue of *Psychiatric Services* includes a special section on the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. It complements a similar special section in the journal last year that covered the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study (1). STAR*D was the largest independent clinical trial ever conducted to study the effectiveness of interventions for people with major depressive disorder who do not respond to an initial antidepressant. This special section provides a summary of findings and a range of commentaries on implications for current treatment and policy. Although the STAR*D trial ended several years ago, it continues to generate interest, especially during a time when community-level treatment data are needed to inform policy decisions about funding mental health services.

In the first article in the special section, Gaynes and coauthors (2) provide a concise overview of the study and its findings. They discuss various limitations that others have identified, but they also delineate results that despite those limitations continue to have relevance for treatment and health policy. One controversial decision was the exclusion of a placebo group. However, a primary goal of the study was to produce data relevant to diverse community populations, and inclusion of a placebo group would have changed the representative nature of the sample by reducing the number of people willing to participate. In addition, STAR*D clinicians' use of a measurement-based system of care does not represent typical community practice. Yet given current attention to paying for performance and the expanding use of electronic health records, the demonstrated effectiveness of such a system could have important implications for future practice.

One of the most discussed topics in the clinical treatment field is the potential for individual treatment options informed by genetic markers. In the second article, Laje and coauthors (3) present an overview of pharmacogenetic findings based on data from STAR*D—nearly 2,000 participants provided researchers with DNA samples. Although the authors' focus on genetics may be rather heavy for some readers, the article provides a good overview of how these data have been used to search for potential links between an individual's genetic makeup and response to antidepressant medications. Unfortunately, no findings have been conclusive, but the work emphasizes the importance of large trials such as STAR*D for informing future efforts in both pharmacogenetics and the pathophysiology of the illness.

Laje and his coauthors' note that although some may criticize the heterogeneous samples used in effectiveness trials such as STAR*D because they make it more difficult to detect genetic effects, it is a necessary "problem" if one is to develop tools that can be used in diverse community populations. The authors also describe several issues, such as assessment of medication adherence and better delineation of phenotypes, that need to be considered if future clinical trials are to have relevance to pharmacogenetics research. This emphasizes the importance of such large clinical trials for a variety of research efforts and the necessity of including all potential players in discussions of future clinical trial designs.

These articles are followed by four commentaries intended to provide a cross-section of opinion on the implications of the STAR*D study from the perspectives of consumers, primary care physicians, payers, and federal research funders. Shern at Mental Health America and his colleague (4) discuss the importance of results from studies such as STAR*D for consumers who live every day with depression. They note that the cost of the study was minimal when compared with the consequences of not funding such research. The commentary by Ong and Rubenstein (5) outlines implications for primary care providers. Most people with depression are seen initially by primary care providers and receive care in their offices. A frequent criticism of primary care providers is that they don't treat depression as well as psychiatrists do. Yet STAR*D findings show that they can achieve the same outcomes as psychiatrists when they use a measurement-based care approach. However, the reality in current primary care practice is that the level of service provided in STAR*D is not the norm. Ong and Rubenstein describe changes that are needed to make the STAR*D approach more feasible in primary care settings.

In the third commentary, Little and her coauthors (6) discuss the payer perspective. STAR*D findings have important implications for the way in which public and private insurers construct formulary coverage. Even more important are the inferences that can be drawn about delivery of care: STAR*D clinicians improved patient outcomes by steadily monitoring and managing care using the

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measurement-based system. In the final commentary, Insel and Wang (7) present the perspective of the federal research agency responsible for funding such research. They argue that research should now move beyond comparing the effectiveness of current medications to developing better and more rapid treatments. The development of new treatments is a laudable goal, but to pursue it at the expense of other clinical research could overlook the reality of current clinical treatment and policy issues as well as the importance of large trials such as STAR*D for informing treatment development.

What is often excluded from discussions about STAR*D and other large clinical trials such as CATIE is the context in which they were initiated and conducted. STAR*D was one of a group of four large trials initiated by the National Institute of Mental Health (NIMH) around the same time in the late 1990s. The other three trials were Treatment for Adolescents With Depression Study (TADS) (8), Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) (9), and CATIE (10). Before their launch, NIMH convened meetings with key constituents to address the types of treatment information needed to inform community practice and health care policy. As part of that effort, NIMH created a subgroup of its National Advisory Mental Health Council that subsequently produced a report, *Bridging Science and Service* (11). On the basis of recommendations from the report and feedback from constituents, NIMH broadened its treatment and services research portfolio to fund studies that would help to answer the critical questions of who requires treatment, what type of treatment they need, and how to ensure that they receive appropriate treatment (12).

A key recommendation was for NIMH to fund large clinical trials that would study the most pressing clinical treatment issues in community practice and do so in a way that would be relevant to the populations seen in community practice (that is, clinical effectiveness trials). NIMH focused on clinical treatment issues identified as most pressing by constituents. One of the goals was to set up a clinical research infrastructure that would be comparable to those available for cardiovascular disease and cancer. This required the contributions of large numbers of people at the research sites and at NIMH. The infrastructure and successful completion of the trials would not have been possible without the expertise and dedication of staff at NIMH and the academic institutions in this federal-academic partnership. It will collapse and will be difficult to restart without continued commitment.

One can argue the various limitations of any study, but results from large-scale clinical effectiveness studies such as STAR*D are critical for informing current and future debates about funding of mental health treatment services. In addition, such studies are essential for ensuring that people who suffer from depression receive the best current treatment options as we await the development of new and perhaps better treatments. These studies build capacity to conduct state-of-the-art clinical research and provide a platform for research that could delineate the pathophysiology and natural history of mental illnesses and lead to new and better treatments tailored to individuals. Future direction in clinical research requires a bold and expansive vision combined with the appropriate level of resources and partnerships between the federal government, academic institutions, and public and private systems to ensure that we do everything possible to provide the best treatments to people who suffer from mental illnesses. STAR*D was a step in that direction.

With the ending of these large clinical trials, many have become concerned about the future funding of large intervention trials. Recently, NIMH funded a new study of interventions for people in the early stages of schizophrenia (Recovery After an Initial Schizophrenia Episode, or RAISE). In addition, NIMH is collaborating with the Department of Defense on a study to identify effective preventive interventions that could alleviate the rising suicide rate among Army soldiers (Study to Assess Risk and Resilience in Servicemembers, or ArmySTARRS). The hope is that NIMH and other federal agencies will continue to realize the value of studies like these and large clinical trials such as STAR*D.

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