Approaches to Multisite Clinical Trials: The National Institute of Mental Health Perspective

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Abstract

The Division of Services and Intervention Research of the National Institute of Mental Health (NIMH) utilizes a variety of methodologies and approaches in the development of its clinical trials program. In this article, we describe the need for large multisite trials; the mechanisms for addressing this need; and the various approaches that have been used. In the course of carrying out this initiative, we have created opportunities for the Institute and its trial investigators to receive advice and input from the field. We describe the role and function of the trial coordinating center and NIMH staff. We identify the first steps to be taken in the initiation of a trial and highlight the opportunity for ancillary studies. Finally, we enumerate some of the pitfalls of large clinical trials and discuss measures taken to anticipate and address them.

Keywords: Clinical effectiveness, public health, NIMH, research strategy.


With the guidance of the National Advisory Mental Health Council (NAMHC), the National Institute of Mental Health (NIMH) has taken on the challenge of enhancing the public health impact of treatment research and improving the outcomes of mental health care. The challenge involves bridging research and community practice, regulatory and public health approaches to research, efficacy and effectiveness studies, and internal and external validity. The process was initiated in 1999, when the NAMHC charged NIMH to enhance the public health value of its treatment research portfolio (NAMHC 1999). With additional resources from generous National Institutes of Health (NIH) budget increases, NIMH expanded its treatment research to include larger scale, public health–oriented treatment studies (Niederehe et al. 1999; Norquist and Hyman 1999; Norquist et al. 1999). These large studies are designed to answer important clinical questions faced in community practice and not answered previously in small, acute treatment trials. The kinds of issues important to community practice include what treatment is best for those who present with multiple conditions, what medication should be used first when there are various choices, what to do when the first intervention does not work, and what the long-term effectiveness of a particular treatment is. To answer these types of questions, studies must include heterogeneous samples of patients, clinicians, and settings of care; simulate actual clinical practice by using sequential treatment strategies and algorithms; and focus on long-term and clinically meaningful outcomes.

In this article we provide the rationale for this new initiative to develop large multisite clinical trials. The small, short-term randomized controlled treatment trial with highly selected subject populations is now regarded as the beginning of the clinical research process and not the end. The ultimate goal of clinical treatment research is to enhance the care of people with mental illnesses, provide tools to families and clinicians, and yield data to support the planning of care within public and private community treatment systems.

In the remainder of this article, we discuss the goals of the expanded clinical trials program, the development of the larger treatment trials, and the new opportunities provided by an expanded research program. Major programmatic developments in basic science and services research should be matched and complemented by significant investment in treatment studies. However, NIMH does not have resources to match the aggregate resources of the pharmaceutical industry for drug development and acute treatment trials aimed at regulatory agencies and the approval process. At the same time, the pharmaceutical industry is not motivated to conduct many studies on the comparative and cost effectiveness of different drugs...
within a class or between classes in the phase IV or post-marketing period. Research that NIMH supports should have a significant impact on community clinical care by expanding on the work supported in the private sector and answering questions not usually considered by industry.

Why Conduct Large Multisite Clinical Trials?

Because large multisite clinical trials are costly and labor-intensive undertakings, it is important to consider what questions they can answer that are not already addressed in trials conducted by industry for drug development, approval, and marketing or in smaller, more focused investigator-initiated studies funded by industry, foundations, or NIMH. Not every question in clinical therapeutics and interventions research requires such an approach (Hogarty et al. 1997). To answer the types of questions that are faced in community practice and affect public mental health (e.g., what treatments are best for the various types of people and comorbid illnesses found in the community, which treatment is best for a specific person given the available choices, how well will interventions work in actual community practice) requires large, heterogeneous populations in various treatment settings. Thus, multiple sites across various community settings with large samples of research participants are needed.

These issues were at the forefront of discussions at NIMH and between NIMH and members of the academic and clinical research communities prior to the launching of our large clinical treatment trials funded under the contract mechanism. The procedure we followed was deliberate, prolonged, open, and responsive to guidance and input at a number of points in the process. In particular, there was substantial opportunity for investigators from the field to advise on priorities and identify important questions. Before issuing contracts for large clinical trials, NIMH wanted to ensure that funding was put into areas that were considered important from a public health perspective and where there was a scientific opportunity to answer pressing clinical questions that had not been adequately addressed by previous studies. A similar approach had been taken by other components of NIH, such as the National Cancer Institute and the National Heart, Lung, and Blood Institute (NHLBI). Over the years, these institutes have maintained large clinical trial programs, which were taken into consideration when launching the NIMH initiative.

A plan for the development of each large clinical trial to be funded under the contract mechanism was developed and presented to the NAMHC for discussion at the public section of its meeting. Each plan was approved by the NAMHC. After further input from the field, NIMH issued a formal request for proposals (RFP) for each trial. This was the basis for proposal submissions, which were reviewed by peer-review committees. After negotiating with those that were found both technically acceptable and had scored in the fundable range, NIMH staff selected applications for funding.

A number of different approaches to the development and administration of a contracts-based approach to large clinical trials were considered. The first approach is one in which staff develop a protocol and investigators submit contract proposals competing to serve as sites for the trial. Clinical coordination, data base management, and statistical analysis are all centralized at an NIMH in-house unit. This approach was used in earlier trials, such as the Treatment Strategies in Schizophrenia study. After consultation with a number of sources within NIH and within the field, we decided against this approach. First, NIMH did not have the personnel to coordinate and manage multiple trials of the size and complexity envisioned for these new initiatives. Second, and more important, we wanted to encourage the development of this capacity among our extramural investigators and give them the freedom to develop innovative scientific proposals to answer the questions posed by NIMH.

Based on the experience of other NIH institutes, we decided to contract with a single extramural coordinating center to manage each trial. The coordinating center would, in turn, contract with sites and oversee the clinical, administrative, data managerial, and analytic aspects of the trial. This approach is similar to the practice of outsourcing in the private sector and significantly augments the internal NIMH capacity. It was used in the three-arm trial of Hypericum perforatum (St. John's wort), a selective serotonin reuptake inhibitor, and placebo in major depression. NIMH initiated the trial in 1997 with funding provided by the NIH Office of Alternative Medicine; the trial was recently completed (Hypericum Depression Trial Study Group 2002).

In our newer large clinical trials, our approach has been to have staff identify the rationale for the trial and the parameters to be considered in its design. A final protocol, however, was seen as the first major product and "deliverable" of the coordinating center. We saw this as a way to leverage the creativity of the research community and encourage major intellectual investment from investigators in the trial. The initial protocols presented as part of the proposals are seen as the beginning of the protocol development process. Early stages of the contract involved continued intellectual input and advice in the preparation of a final approach to the study. We adopted this approach in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) contract awarded in 1998 to the...
Massachusetts General Hospital with Gary Sachs, M.D., serving as principal investigator. The contract for the Treatment for Adolescents with Depression Study (TADS), awarded to John March, M.D., of Duke University in 1998, adopted the same approach. We used this approach in two other trials awarded in 1999, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), directed by Jeffrey Lieberman, M.D., of the University of North Carolina; and Sequenced Treatment Alternatives to Relieve Depression (STAR*D), directed by A. John Rush, M.D., of the University of Texas Southwestern Medical Center.

Some colleagues recommended that we contract separately for protocols and trial coordination. The reason for this was obvious: some investigators might be better at the conceptual work of protocol development and others at the operational work of trial coordination. The colleagues suggested that NIMH contract for each protocol, select the best one or construct the best one from pieces of those submitted, and then solicit proposals to coordinate the trial for that protocol. This proposed approach broke down over issues of the intellectual property rights of investigators. Under this approach, it was appropriate to contract for a protocol from investigator A and then turn that protocol over to, possibly, another investigator, B, for study. We were sensitive to the need to guarantee that investigator A's intellectual contribution would be recognized and credited throughout the project. Although this approach is certainly allowable in contracting law and policy, it does not reflect the usual research practices of the research community and is not characteristic of the collegial and collaborative relationship between NIMH and the field.

The topics chosen to be studied were those considered to have high public health importance and to have been inadequately addressed by previous research. In addition, NIMH wanted to create the capacity to recruit large numbers of people from diverse settings and backgrounds. The intention was to create opportunities to answer immediate clinical and services research questions in these illnesses and to provide for future long-term studies that might answer questions only addressable by following large treated populations over time. In addition, these large networks of sites were considered essential to the development of future clinical research programs and infrastructures. This effort was patterned on the way that many of the other institutes at NIH (e.g., NHLBI) have addressed clinical treatment issues and built clinical treatment research capacity in their fields.

Since the initiation of the large trials, representatives from the trials and NIMH have made a large number of presentations at national scientific and professional meetings, such as the NIMH-sponsored New Clinical Drug Evaluation Unit meeting, the fourth International Confer-

ence on Bipolar Disorder, and the annual scientific meetings of the American Psychiatric Association, the American Association for Geriatric Psychiatry, and the American Public Health Association. Trial principal investigators (PIs) have prepared design papers and early descriptive papers for submission to appropriate scientific journals.

What Mechanisms Are Available?

Although the primary emphasis of this initiative was to establish large clinical trials funded under the contract mechanism, NIMH continues to appreciate the importance of investigator-initiated research proposals. In fact, NIMH has encouraged the field to develop new studies to address the various treatment issues still paramount in the mental health field. A number of large multisite treatment trials have now been submitted under the grant mechanism. Below, we first describe the process for funding applications under the contract mechanism. Because NIMH is not likely to issue any new contracts in the foreseeable future, we focus the rest of this section on applications that would be investigator initiated.

Contracts. A contract is typically used to conduct research of an urgent public health concern that has not been addressed and is considered unlikely to be addressable through regular investigator-initiated mechanisms. In these cases, the Institute issues an RFP, which outlines the work to be done under the contract. This outline may include a detailed research protocol to be conducted under the contract or simply indicate only in general terms the research questions and objectives to be addressed. The RFP requires funds to be set aside for that project. Proposals must include both a description of the research approach (technical proposal) and a budget (business proposal). The technical proposals are peer-reviewed by a special committee whose reviewers have no access to the business proposal (to establish the scientific merit of the proposed research without any possible interference from cost considerations). The NIMH contract office considers only proposals whose scientific content is deemed adequate by the review committee. Selection of a proposal for funding is determined by considering the scientific merits, the operations capability of the team, and the cost of the proposed study. NIMH staff conduct the final phase of the selection process. Although cost considerations are important in the final decision, the scientific value of the proposal (as captured in the peer-review process) and operations capacity remain paramount. Unlike with grants and cooperative agreements, no funds are transferred to the winning contractor upon contract award. At that time, NIMH agrees only to compensate the contracting institu-


tion for relevant research activities during the contract period. Only work that is actually done can be submitted to NIMH for payment.

From this brief description, it is clear that the Institute maintains much closer involvement and much tighter control of research funds under a contract mechanism. In addition, a contract can be more easily terminated than any grant mechanism for nonperformance or other technical reason. It is possible to award separate contracts to each site of a research network, or to award just one contract to one coordinating site, which then subcontracts to the various sites. The former model was used for the Research Units on Pediatric Psychopharmacology (RUPP), a network for multisite clinical trials of psychotropics in children and adolescents (RUPP Anxiety Study Group 2001; RUPP Autism Network 2002). Examples of the latter model are the H. perforatum study in depression, TADS, CATIE, STEP-BD, and STAR*D.

Cooperative Agreements. For research areas or specific research questions that have high public health importance, have not been addressed through investigator-initiated research, and require direct involvement of NIH staff to be properly monitored and conducted, an institute can consider issuing a request for applications (RFA) for a cooperative agreement (a U mechanism). Typically, U applications are due on a date that is different from that for the other grant applications, and a special committee is appointed to review U applications.

A cooperative agreement can fund a specific project or support the research infrastructure for multiple projects. An example of the former is the Multimodal Treatment of Attention Deficit Hyperactivity Disorder (MTA) study, which was awarded to six clinical sites in 1992 (MTA Cooperative Group 1999). The study allowed the rapid enrollment of a total sample of 579 children who were treated for 14 months. In this study, all the steps of protocol development and data collection and analysis were supported by NIMH. An example of utilization of the cooperative agreement for supporting infrastructure is the recently awarded RUPP and Psychosocial Interventions network (RFA-MH-02-002, August 31, 2001). With this initiative, NIMH supports a network of clinical sites properly staffed to conduct research on pharmacological and psychosocial treatment interventions for children and adolescents, with funds for specific protocols of high public health relevance.

In cooperative agreements, NIMH staff are directly involved with the grantees in all the major phases of the research activities. Administratively, however, despite this high level of NIH involvement, cooperative agreements are still grant mechanisms. Once awarded, funds are transferred to the PI’s institution at the beginning of each funding year and are administered locally, similar to procedures for an R01.

In some situations, investigator-initiated grants to support complex multisite clinical trials in areas of high public health importance or sensitivity are converted by NIMH into cooperative agreements to allow direct involvement of NIMH staff in the conduct of the study. Usually, a group of investigators submits a collaborative R01 for a multisite trial, which is then converted to a cooperative agreement by NIMH once it is chosen for funding.

Grants. The classic investigator-initiated R01 can be used to support a multisite study. Two approaches can be considered. The collaborative R01 is appropriate when the proposed study requires more than one site. The program announcement “Collaborative R01s for Clinical Studies of Mental Disorders” (available on-line at www.nih.gov/grants/guide/pa-files/PA-01-123.html) illustrates the conditions under which such a grant application might be considered. Typically, the applicants are two or more PIs who are at different clinical sites and submit the same study protocol. The coordinating functions and data management can be included in one of the applications or as a separate R01 application within the same collaborative R01. In the former scenario, the clinical data-gathering sites must be separate from the coordinating protocol-monitoring component to ensure independent oversight of the study. Besides these organizational aspects, the content of the application varies little across sites, the differences being limited to site-specific personnel and budget issues. Collaborative R01 applications are reviewed together, and the reviewers consider the multisite study in its entirety. There is, however, no overall priority score for the whole project. Rather, each applicant receives a priority score based on the strengths and weaknesses of the individual application. Thus, it is possible for the applicants of the collaborative R01 to get different priority scores, even though the tendency of the initial review groups has been to assign the same score to all applicants.

The alternative approach to funding an investigator-initiated multisite trial is to submit a single R01 that includes subcontracts to a network of clinical sites. Under this model, there is only one grant that is being awarded, assuming a successful review process, to one PI who is responsible for organizing and conducting the study. Administratively, the investigators at the sites operate as contractors to the study PI, who has the authority to terminate their contracts and replace them with other sites. It is clear that this second approach is much more hierarchically organized than the collaborative R01.

These two models have their advantages and disadvantages. A collegial interaction among the study PIs can...
be more easily envisioned with a collaborative RO1 in which each study PI is an NIMH grantee with an individual RO1 award. Some studies may, however, require centralized integration of the various parts of the project, and this can be more easily achieved with a single RO1. It should be noted that intermediate approaches between collaborative and single RO1s are also possible. For instance, two or more PIs can apply for collaborative RO1s for a study that will involve other sites under contract from the applying PIs. As is the case with any other investigator-initiated grants, NIMH staff can provide technical assistance in the pre-award phases, but they are not involved in the research activities once the grant is awarded. Once the grant is awarded, the degree of monitoring and control that NIMH can exercise is limited. Projects that necessitate considerable investment of public funds can, as noted above, be converted to cooperative agreements (U01) to increase NIMH involvement in the operations and oversight of the study.

Both the collaborative RO1s and the RO1s with multiple sites under contract with the grant PI are likely to cost more than the typical RO1 for single-site projects. If the estimated direct cost of the entire study is $500,000 or greater in any single year of the funding period, the grant application is classified among the "special actions" for NIH administrative purposes. The NIH policy on this matter was published in March 1998 (available on-line at www.nih.gov/grants/guide/notice-files/not98–030.html) and revised in October 2001 (available on-line at grants2.nih.gov/grants/guide/notice-files/NOT-OD–02–004.html). Because these projects require commitment of considerable resources from the funding institute, the investigator(s) must send a letter of intent to relevant program staff at NIMH 6 weeks prior to the application deadline, briefly outlining the proposed study and estimated costs. The investigator must justify the need for a large study of the particular question, the study’s relevance to the programmatic priorities of NIMH, and the study’s uniqueness, cumulativeness, and contribution to the field. The investigator must also provide a budget justification and discussion of study operations. NIMH staff review such requests in light of program needs and estimated funding availability. Following a successful NIMH internal review, prospective applicants are sent a letter approving the grant submission. Only grant applications that have been approved in this way by NIMH can be reviewed by the initial review groups. This process permits the Institute to avoid duplication of similar costly efforts and spares investigator time and effort in areas unlikely to receive funding. Moreover, while some RO1 applications for multisite trials can be reviewed by the standing NIMH Intervention Review committee, others require special ad hoc review groups whose constitution must be carefully arranged. Prospective applicants consult with NIMH staff as early as possible when planning such grant applications.

Coordinating Center Functions

The functions of a study coordinating center (CC) in any of the above mechanisms are by definition multifold. The CC may be responsible for such tasks as preparing (or finalizing) the study protocols, selecting the clinical sites where patients are enrolled, training the staff, designing the clinical research records, preparing the study medications, providing the software for data entry, managing the randomization of sites or subjects, ensuring the quality of the data base, monitoring adherence to the protocol, ensuring the safety of the study participants, and arranging for data analyses and reporting.

The CC is charged with planning, organizing, and running the study in all its details. To this end, it must have staff with diverse and adequate expertise in clinical trial design, statistics, data management, and safety monitoring, and technical staff must be willing to commit a substantial amount of their time and effort to the project. At times, all these functions can be found in one institution. More often, the CC is formed by combining expertise from several sources, sometimes including contract research organizations. In the past, NIMH staff performed many of these functions. However, because of the increase in the number and size of the current clinical trials, NIMH now has the resources to provide only occasional technical assistance and monitoring.

Ancillary Studies

Once the four large contracted clinical trials (TADS, STEP-BD, CATIE, and STAR*D) were awarded, it became clear that they provided an opportunity to address a number of questions not considered in the original RFP. NIMH regards the pool of subjects and sites as unique national resources for other clinical, basic, and services research studies. Each trial is a platform or infrastructure that facilitates the development of new research and expands the capacity of the investigators directly involved in the trial. Ancillary studies can be proposed by any investigator and are not limited to those participating in the trial itself. Thus, rather than concentrating resources, we expect these trials to increase the capacity of the field and to provide opportunities for individual research projects. It is important to note that ancillary studies, as referenced here, are possible in only the four large contracted clinical trials.

Certain topics are seen as sufficiently important to merit a centralized approach to ancillary studies. This was
Clearly favor one approach in a series of cumulative testing decision options that are no longer first choice options. Similarly, a proposed trial may begin too late. Following Kraemer (2000), we recognize that there are alternatives to intervention, or where a meta-analysis will not sufficiently crystallized to generate clear decision most, the trial might be premature, with the state of the art and that they produce data to inform treatment in the community. To accomplish this goal, the NAMHC formed a workgroup in 2002 to review the portfolio of

Pitfalls

Following Kraemer (2000), we recognize that there are several potential pitfalls of a multisite trial. First and foremost, the trial might be premature, with the state of the art not sufficiently crystallized to generate clear decision options. Similarly, a proposed trial may begin too late, testing decision options that are no longer first choice alternatives to intervention, or where a meta-analysis will clearly favor one approach in a series of cumulative studies. We see these largely as conceptual problems that can be identified early through the many review and advisory steps we complete prior to issuing the formal RFP or funding a grant.

Kraemer notes that an ineffective decision structure containing too much or too little internal communication can compromise a trial’s results. A potential problem in all studies, the problem can be magnified in large multisite trials, so investigators, staff, and advisors work hard to maintain appropriate internal communication. They also monitor external communication, making sure that procedures exist to ensure that information about the trial is accessible and consistent. We believe that principal spokespersons for the trial are the PI/study chair and the government project officer and that all communications should go through them or be delegated by them to someone else for a specific purpose.

Kraemer also notes the special challenges involved in data analysis and treatment recommendations when site differences are ignored or when there is a premature closure of analysis. We agree that this is critical and look to the NIMH Data and Safety Monitoring Board and external advisors to make sure that we deal with these issues appropriately. In addition, recruitment is a frequent concern in large trials. NIMH has undertaken a variety of new efforts to ensure that the anticipated numbers of research participants are attainable in any of the proposed trials.

Ongoing Oversight of Clinical Trials

With the guidance of the NAMHC, NIMH developed a collaborative approach for ongoing oversight of the clinical trials program. As part of this oversight, we have engaged investigators from the field and from other NIH institutes as we attend to scientific and operational issues in each trial. In each of the large contracted clinical trials, NIMH will from time to time call upon independent experts to provide opinions about the trial’s progress. Likewise, in collaborative grants that have been converted to cooperative agreements, NIMH will, as needed, call upon external advisors to comment on the progress of the proposed studies.

The majority of funding is devoted to investigator-initiated grants. To ensure the maximum public health benefit of these studies, NIMH must try to reduce duplication of efforts and broaden its treatment portfolio to take advantage of scientific opportunities in clinical research. In addition, it is imperative, given the resources involved and the commitments by research participants, that the studies be completed successfully and that they produce data to inform treatment in the community. To accomplish this goal, the NAMHC formed a workgroup in 2002 to review the portfolio of
clinical treatment trials currently funded under grants to assess progress achieved to date, to identify critical knowledge gaps and scientific opportunities for future trials, and to provide guidance concerning oversight for clinical trial performance. The workgroup—which consists of NAMHC members, extramural experts in clinical treatment trials, statisticians, consumers, and providers—is expected to issue a report to the full NAMHC at the May 2003 meeting.

Conclusion

Contracts account for about 20 percent of the budget for interventions research and represent only one approach to the support of multisite trials. About 80 percent of NIMH funds for intervention research go to support investigator-initiated studies. We expect that these proportions will remain roughly the same in the future. The trials funded under contracts have clearly not answered all the questions about treatment for illnesses that can be addressed within the infrastructures that have been created for the current trials. We are addressing first order-type matters: what approach to treatment works best for what kinds of patients in what kinds of settings. The results will guide us to many new questions, such as how long to treat, how to enhance adherence, how to implement approaches to treatment, how to approach rational polypharmacy, how to deal with residual symptoms and disabilities, and what kind of preventive treatment is possible.

Large multisite trials represent new opportunities for research to answer important questions that immediately and greatly affect public mental health. Their infrastructures offer valuable platforms for future work in the respective illnesses. They build upon the important body of knowledge in basic science, treatment development, and services research and carry our work to a new level of public health relevance. The potential of these trials to improve community care is enormous. At the same time, these trials provide the context for more intensive, investigator-initiated basic and clinical studies of etiology, pathophysiology, natural history, delivery of services, and outcomes of care. This is an important new development for our field, and we look forward to significant interaction with the research community on matters of conceptualization, design, and implementation of future investigator-initiated trials.

References


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Minority Research Training in Psychiatry

Through a five-year, $2.5 million grant from the National Institute of Mental Health, the American Psychiatric Institute for Research and Education (APIRE) is seeking through the Program for Minority Research Training in Psychiatry (PMRTP) to increase the number of minority psychiatrists entering the field of psychiatric research.

The program provides medical students with funding for stipends, travel expenses, and tuition for an elective or summer experience in a research environment, with special attention paid to trainees’ career development in research. In addition, stipends are available for a limited number of one- or two-year postresidency fellowships for minority psychiatrists. Residents may engage in full-year research training during the last year of psychiatric residency or in “year off” research training.

Training takes place at research-oriented departments of psychiatry in major U.S. medical schools and other appropriate sites throughout the country. An individual at the site (the research “mentor”) is responsible for overseeing the research training experience.

Administered by the American Psychiatric Institute for Research and Education, the program includes outreach efforts to identify minority medical students and residents who are potential researchers and to put them in touch with advisors who counsel them about careers in psychiatric research. Additional activities assist fellows and alumni in their research career development.

The director of the PMRTP is James Thompson, M.D., M.P.H.; the project manager is Ernesto Guerra. An advisory committee of senior researchers and minority psychiatrists developed guidelines for applicants and criteria for selection. The members of this committee evaluate and select trainees, oversee the research training experiences, and play a role in evaluating the effectiveness of the program.

December 1 is the deadline for applications for residents seeking a year or more of training and for postresidency fellows. For medical students, applications are due three months before training is to begin. Summer medical students who will start their training by June 30 should submit their applications by April 1.

For more information about the PMRTP, call the toll-free number for the PMRTP, 1-800-852-1390, or 202-682-6225, e-mail eguerra@psych.org, or write to PMRTP at the American Psychiatric Institute for Research and Education, 1400 K Street, NW, Washington, DC 20005.