Treatment Research in Mental Illness: Improving the Nation's Public Mental Health Care through NIMH Funded Interventions Research

Report of the National Advisory Mental Health Council's Workgroup on Clinical Trials

EXECUTIVE SUMMARY

The mission of the National Institute of Mental Health (NIMH) is to reduce the burden of mental illness and behavioral disorders on the people of the United States through research on mind, brain and behavior. An important corollary of this mission is to improve the treatment of these disorders. A critical activity in accomplishing this mission is developing and optimizing the use of treatments for mental illnesses in the U.S. The NIMH, through the Division of Services and Intervention Research (DSIR), funds well over 100 treatment studies, many involving multiple sites, addressing important clinical questions that go beyond the scope and mission of the clinical trials conducted by the pharmaceutical industry in the private sector. These clinical trials are funded largely through investigator-initiated grants, but also through cooperative agreements and research contracts. In addition, training grants support the career development of aspiring investigators in clinical treatment research. The scope of these trials covers all of the disorders in the NIMH purview, across the entire lifespan, including a diverse set of populations and employing an array of research designs and methodologies for studies of proof of concept, evaluation of efficacy/safety, and treatment effectiveness.

The NIMH is interested in supporting innovative therapeutics and interventions research, but in the context of finite resources, support must be focused strategically. The strategy must be determined by research gaps, scientific readiness, and public health priorities. Ensuring the maximum public health impact of NIMH treatment initiatives also requires considering issues of duplication, overlap and conflict with existing publicly and privately funded programs as well as the competition for available pools of research participants and balance across clinical content areas.

To ensure that the NIMH's treatment research portfolio is meeting the needs of the field while making the most efficient use of allocated resources, Dr. Thomas Insel, Director of the NIMH, reconfirmed an earlier plan for the National Advisory Mental Health Council (NAMHC) to review the Institute's extramural clinical trials portfolio currently funded by the NIMH DSIR.[1] For this purpose, the NAMHC established the Council Workgroup on Clinical Treatment Trials, which reviewed the extramural treatment portfolio within

[1] NIMH funds a broad array of clinical research in its extramural and intramural programs, but the Workgroup's charge was limited to the extramural treatment trials.

the DSIR for balance, scientific quality and relevance, and paid particular attention to the operational issues specific to multi-site clinical trials[2] funded through the grant mechanism, which the Workgroup determined warranted additional review.

Based on its review, the Workgroup strongly endorsed the important role of the NIMH in fostering treatment research in mental disorders ranging from facilitating treatment development to evaluating the efficacy, safety and effectiveness of treatments, to providing an essential complement to the extensive treatment research efforts of the pharmaceutical industry. In general, the Workgroup felt that the investigator-initiated treatment research grant portfolio of DISR reflected reasonable balance and proportional diversity across the mental disorders. This balance was also reflected across the various somatic, pharmacological, and psychosocial treatment modalities for the treatment of mental disorders and behavioral disturbances. However, there were also areas where significant treatment questions appeared well addressed (e.g., electroconvulsive therapy), those where more study is essential (e.g. treatment adherence, polypharmacy), and those where the questions are no longer current (e.g., tardive dyskinesia). Further, too few studies were innovative and of potentially high impact on clinical practice. Similarly, a concern was expressed about the congruence of the research portfolio with the major questions confronted by mental health care providers on a daily basis. Notable exceptions to this concern were the contract-supported multi-site “practical trials” in bipolar disorder, major depression and schizophrenia which employed hybrid study designs, as well as the more recent multi-site intervention trials funded through the cooperative agreement mechanism that are focusing on clinical questions faced by community providers. The Workgroup thought these trials represented what should be an important segment of the NIMH treatment portfolio. The Workgroup endorsed recent efforts by DSIR staff to improve the public health relevance of treatment studies and encouraged an even more active staff role in initiating studies of public health importance through the cooperative agreement or contract mechanism when investigator-initiated grants are not likely to address such issues.

Moreover, concern was expressed about the failure of too many investigator-initiated grants to meet their overall and minority enrollment targets on time, as well as the validity of these targets. The Workgroup encouraged efforts by the DSIR staff to improve recruitment through consultation with investigators and by assuming a more direct collaborative role through the cooperative agreement and contract mechanisms. More involvement by NIMH staff has appeared to help performance of many studies.

The Workgroup also thought that more could be done to maximize resources by creating enduring core resources, procedures, and infrastructures that would facilitate treatment studies. The Workgroup concluded that more should be done to encourage researchers to report their results with attention to clinical and policy significance, in addition to statistical significance.

[2] A multi-site trial is a study conducted in more than one location with different investigators sharing common procedures and designed to answer the same research question. The multi-site trial may be funded as a contract, grant, or cooperative agreement.

Following its review of the portfolio and the special issues relating to multi-site clinical trials, the Council Workgroup concluded that there were a number of cross-cutting issues that the NIMH should address to further improve the Nation's mental illness treatment research enterprise including the expansion of its treatment development capacity and clinical trials infrastructure as called for by the NIH Roadmap. These recommendations, divided into three main areas, are listed here.

CREATING THE OPTIMAL TREATMENT RESEARCH PORTFOLIO

Treatment research in mental illness has some inherent differences from other forms of biomedical research and entails some unique challenges that must be overcome. Moreover, treatment research conducted by the pharmaceutical industry typically differs in fundamental ways from the kinds of studies that are required to inform mental health care providers, administrators and policy makers. Finally, to answer many questions in the treatment of mental illness, studies of great complexity and scale are required that often exceed the capacities of any one investigator or institution to conceive and orchestrate individually. The NIMH has already launched an effort to answer important clinical therapeutic issues through the funding of large clinical trials under the contract mechanism. However, the NIMH should adopt a more proactive strategy to further develop its treatment research programs and ensure that the most important clinical therapeutic and public mental health issues are addressed in a methodologically rigorous and ecologically informative manner. This is especially important if NIMH wants future investigator-initiated grants to address these pressing clinical issues. To do this, the Workgroup makes the following recommendations:

Recommendation 1: The NIMH should establish a process to seek input from various stakeholders that will inform the direction of future treatment research, determine what studies are most needed and integrate public health interests with scientific opportunities.

Recommendation 2: The NIMH should consider new ways to expand the development of innovative psychosocial, psychopharmacological and somatic treatments. Although existing treatments have been enormously successful and have great potential to decrease burden of mental illness, they have clear limitations and there are enormous unmet therapeutic needs. Consequently, innovative treatments must be developed based on new findings in basic neuroscience and behavioral science research. To attain these goals, the NIMH should foster research ranging from treatment development to assessment of treatment efficacy/safety and effectiveness using the optimal research designs and methodologies of treatment research. To implement such research the NIMH should employ various mechanisms, including program prioritization, requests for applications, program announcements, and contracts.

Recommendation 3: The NIMH should continue to expand efforts, informed by a previous Council report (*Bridging Science and Service*), to fund treatment research that optimizes existing treatments and facilitates their integration in the range of healthcare settings. Such research should include larger community focused trials with hybrid designs that attempt to maximize the generalizability of the findings. These efforts should

be informed by clinical and services researcher expertise, as well as consumer, provider and payor stakeholders to ensure that they are relevant to the needs of the community.

BUILDING CLINICAL TRIALS CAPACITY AND EXPERTISE

Adequate resources to conduct treatment research are required to advance knowledge in therapeutics and to translate it to improved care. Consistent with the NIH Roadmap emphasis on facilitating the development of new treatments and enhancing the clinical research enterprise to evaluate therapeutic agents and modalities, the Workgroup recommends the following actions:

Recommendation 4: The NIMH should develop and maintain large networks of sites reflecting community populations and relevant healthcare systems to answer important public health questions where investigator-initiated grants or pharmaceutical trials are not likely to produce studies of sufficient size and scope to provide robust answers.

Recommendation 5: The NIMH should expand its efforts to involve historically under-represented populations in clinical research including women, ethnic and racial populations, and children and the elderly.

Recommendation 6: The NIMH should issue special career development award and training announcements to increase the number of investigators capable of conducting clinical treatment research in mental illness.

Recommendation 7: The NIMH should facilitate research by standardizing data acquisition and developing central data repositories to make data from completed studies more widely available for scientists and the public.

Recommendation 8: The NIMH should support the development of core resources to facilitate the capacity of investigators, particularly young investigators or investigators lacking research experience and infrastructure, to conduct treatment research. These resources might include study coordination, community engagement training, data management, statistical planning and analyses, as well as data and safety monitoring.

Recommendation 9: The NIMH should encourage innovative research designs, high impact studies, and the development of the large trial networks and core resources to enhance the science and public health value of clinical trials research.

Recommendation 10: The NIMH should seek to partner with other agencies to facilitate the development and optimization of treatments potentially including the Food and Drug Administration (FDA) and the Substance Abuse and Mental Health Services Administration (SAMSHA), as well as the pharmaceutical industry.

Recommendation 11: The NIMH should seek to improve the translation of clinical trials research results into clinical practice.

IMPROVING THE OPERATION, EFFICIENCY AND PRODUCTIVITY OF CLINICAL TRIALS

Clinical research and the clinical trials program of NIMH are important and expanding enterprises of mental health research. Thus, it is critical to improve the scientific and operational efficiency through cooperation between NIMH staff and investigators. To ensure that the opportunities for successful studies are realized, the Workgroup recommends the following actions:

Recommendation 12: The NIMH staff with relevant expertise in clinical trials should work with all potential grantees as they develop their research applications.

Recommendation 13: Applicants should provide information outlined in the guidance developed for this report (Appendix C). If permissible at NIH, failure to provide this information should be grounds for non-approval to submit an application with costs of $500,000 or greater. If not permissible, the reviewers and NIMH staff should consider these issues in the review and award of the study.

Recommendation 14: IRG review of grant applications for treatment research should take into account the overall competence and expertise of the investigators to conduct clinical trials. Review should include specific comments related to the operational capability of the project and should be considered in the overall scoring of the application.

Recommendation 15: The NIMH staff should scrutinize the operational feasibility of a study and recommend to the NAMHC low funding priority for those proposed studies when there is evidence that successful implementation is unlikely.

Recommendation 16: The NAMHC should consider the public health importance and NIMH portfolio balance of the proposed study in considering low or high funding priority.

Recommendation 17: The NIMH should systematically consider converting large complex treatment studies into cooperative agreements. The cooperative agreement mechanism facilitates cooperation between NIMH and grantees as a means of improving efficiency and performance.

CHAPTER I
COUNCIL WORKGROUP ON CLINICAL TRIALS

The mission of the National Institute of Mental Health (NIMH) is to reduce the burden of mental illness on the people of the United States through research on mind, brain and behavior. An important corollary of this mission is to improve the treatment of these disorders. The NIMH process of developing and evaluating treatments for mental illness occurs in the context of a parallel enterprise for treatment development in the private sector. The pharmaceutical and biotechnology industries support and conduct the preponderance of treatment research in the U.S. and indeed throughout the world. Although these efforts have produced an impressive array of medications that are commercially available for clinical use, it is abundantly evident that a great need still exists both for new and better treatments and for ways in they can be delivered more effectively and economically.

The responsibility for providing and optimizing treatments for mental illnesses in the U.S. falls largely to the NIMH. It has become clear to the scientific community[3] and the leadership of the NIMH[4] that the U.S. clinical research system must be recast to more effectively translate the advances of basic science research to the process of mental health care service delivery and thus improve the standards of care for patients. This awareness was reflected in an earlier National Advisory Mental Health Council (NAMHC) report (see footnote 3). In addition, the leadership of the National Institutes of Health (NIH) has more recently made this recasting, or re-engineering, of the clinical research enterprise a national priority in the NIH Roadmap for medical research in the 21st century[5]. This re-engineering, which NIMH is part of, will include bolstering the nation's clinical trials infrastructure and developing a national clinical trials research network that would be connected by the National Electronic Clinical Trials and Research Network (NECTAR).

Treatment represents the fruition of all forms of biomedical research including basic and clinical research. Treatment trials are critical in determining the efficacy and safety of treatments and their comparative effectiveness in community populations with mental illnesses. The vast majority of treatment research in the U.S. is supported by the pharmaceutical industry, whose purpose in conducting these trials is to obtain regulatory approval by the Food and Drug Administration (FDA) and to address post-marketing questions and marketing related issues. These studies primarily examine the short-term efficacy of medications. However, this activity falls far short of the public health need to optimize treatment effectiveness for community populations and to reduce costs of treatment to the delivery system and the care recipient. It is the responsibility of the NIMH, through the Division of Services and Intervention Research (DSIR), to address

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[3] Tunis, S.R., Stryer, D.B., and Clancy, C.M. *Practical Clinical Trials: Increasing the Value of Clinical Research for Decision Making in Clinical and Health Policy*. **JAMA 290**:1624-1632, 2003.
[4] National Advisory Mental Health Council. *Bridging Science and Service: A Report by the National Advisory Mental Health Council's Clinical Treatment and Services Research Workgroup.* NIH Publication No. 99-4353, 1999.
[5] http://nihroadmap.nih.gov/

the gap between regulatory trials and public health needs.[6] To accomplish this, the DSIR funds well over 100 clinical trials, many involving multiple sites, which address important clinical questions that go beyond the scope and mission of the clinical trials conducted by the private sector. These clinical trials are funded largely through investigator-initiated grants (i.e. R01, R34 and P30 Center grants) but also through cooperative agreements and research contracts. In addition, career and training grants (K awards and T32 institutional training grants) support the development of aspiring investigators in treatment research. The scope of these trials covers all of the disorders in the NIMH purview, across the entire lifespan, and includes a diverse set of populations. The NIMH is interested in supporting innovative therapeutics research, but in the context of finite resources, support must be based strategically on needs as determined by research gaps and opportunities extant at any particular time. Ensuring the maximum public health impact of NIMH initiatives also requires considering issues of duplication, overlap and conflict with existing publicly and privately funded programs, as well as the competition for available pools of research participants and balance across clinical content areas.

To make certain that the NIMH's treatment research portfolio is meeting the needs of the field while making the most efficient use of allocated resources, Dr. Thomas Insel, Director of the NIMH, reconfirmed an earlier plan for the NAMHC (see Appendix A for membership) to review the Institute's clinical trials portfolio currently funded by the NIMH Division of Services and Intervention Research. For this purpose, the NAMHC established the Council Workgroup on Clinical Trials. This report presents the results of the Workgroup's deliberations, analysis, and recommendations for action. In addition to reviewing the NIMH's treatment portfolio in DSIR for balance, scientific quality and relevance, this report pays particular attention to the operational issues specific to investigator-initiated multi-site clinical trials. The Workgroup determined that these issues merited additional review, and offered recommendations for addressing them. The Workgroup was composed of NAMHC members and external participants (see Appendix B for membership) with various types of expertise in mental health care research and service delivery. Council Member Dr. Jeffrey Lieberman served as chair of the Workgroup. In addition, the Workgroup received substantial support from NIMH staff members in DSIR.

[6] NIMH funds a broad array of clinical research in its extramural and intramural programs, but the Workgroup's charge was limited to the extramural treatment trials.

CHAPTER II
THE WORKGROUP'S CHARGE AND PROCESS

WORKGROUP CHARGE

The NAMHC agreed to form a Workgroup to review the portfolio of extramural clinical treatment trials currently funded by NIMH's DSIR in light of scientific opportunities and public mental health priorities. This review was to include:

- Assessment of the balance and relevance of the portfolio to public mental health needs and burden of illness of the nation;
- Identification of critical knowledge gaps and scientific opportunities;
- Assessment of progress to date achieved by extant grants and contracts;
- Provision of guidance concerning oversight of clinical trial performance sites and development of guidelines for management of site non-performance;
- Recommendations to address gaps and deficiencies and to inform development and implementation of future treatment research initiatives; and
- Suggestions for additional Council activities in advising the Director of NIMH regarding treatment initiatives.

WORKGROUP PROCESS

The Workgroup was convened and began its efforts in May 2002. Over the subsequent months, the Workgroup engaged in a series of activities, assisted by NIMH staff, to meet its charge. These activities included:

- Meetings, both in-person and via teleconference, to discuss priorities and determine and assign review responsibilities to Workgroup members
- Obtaining materials and additional information from the NIMH Division of Services and Intervention Research
- Reviewing the NIMH clinical treatment trials portfolio for content and balance
- Convening presentations on the burden of illness and the NIMH portfolio by program staff
- Reviewing NIMH staff proposals for a process to establish portfolio balance and for ways to ensure the successful operations of treatment studies
- Development and discussion of recommendations to NIMH

Materials used by the Workgroup included:

1. Data on the epidemiology and burden of mental illnesses
2. The total roster of grants funded in DSIR by disorder, patient population, treatment modality, and costs
3. Abstracts of the funded treatment grants
4. Lists of non-funded applications

5. Descriptions of research programs in DSIR
6. Descriptions of current large contracted clinical trials
7. List of career (K) awards and institutional training grants in the treatment area
8. NIMH strategic plan for mood disorders
9. CONSORT guidelines (http://www.consort-statement.org/)
10. Information on participant recruitment success in funded grants
11. Summary from program staff of potential reasons certain areas are not being funded – i.e., what have we learned about why certain topics are not supported while others are
12. Summary from program staff of potential reasons that some grants are having performance problems
13. Progress reports from selected poorly performing grants

Based on its review, analysis and discussions, the Workgroup then developed the series of cross-cutting recommendations detailed in Chapter VI. The Workgroup also developed recommendations concerning specific portions of the clinical trials portfolio, and these are detailed in the appropriate portfolio review sections of Chapter IV. In addition, the Workgroup and DSIR program staff conducted a specific review of multi-site studies and have developed specific recommendations regarding such trials. These are presented in Chapter V.

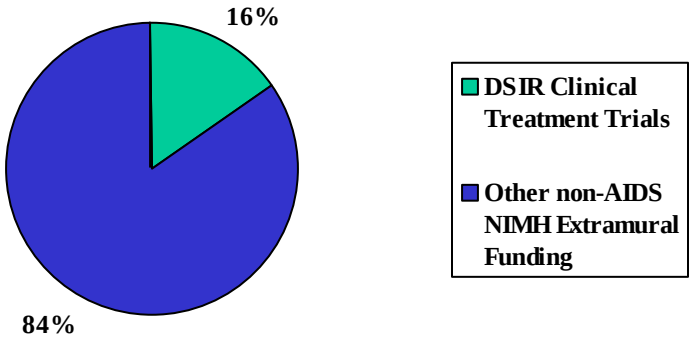
CHAPTER III
THE FY 2003 DSIR CLINICAL TREATMENT TRIALS PORTFOLIO

The Workgroup asked DSIR staff to compile data on the number of non-AIDS clinical treatment trials funded extramurally and the funds it disbursed for those projects. Those data are presented in this chapter, accompanied by a brief description of overall portfolio balance. After this snapshot of the fiscal year 2003 (FY03) portfolio, the chapter continues with the Workgroup's assessment of each disease area's coverage in clinical trials, along with recommendations related to specific segments of the portfolio.

OVERVIEW OF FY03 SUPPORT

Of the total NIMH non-AIDS extramural research budget[7], approximately 16 percent went toward clinical treatment trials supported as Research Project Grants (RPG), contracts, or research centers in DSIR (Figure 1). The $105.5 million spent on treatment trials in FY03 by DSIR included six contracts accounting for $34.2 million. In addition, since the treatment centers provide infrastructure support for treatment trials the 11 treatment research centers are included with combined funding in FY03 of $15.9 million. Thus, the total funds allocated by the DSIR in FY03 on extramural clinical treatment trials research were $121.4 million.

Figure 1: Proportion of the FY03 non-AIDS NIMH Extramural Funding in clinical treatment trials supported as RPGs, contracts, and centers in DSIR.



The RPG and contracts portion of the extramural clinical treatment trials portfolio in DSIR was further examined by disorder (Table 1, Figure 2). Depression trials accounted for 41 percent of this portfolio in terms of number of projects as well as 41 percent of the funds spent in FY03. Treatment trials for bipolar disorder represented nearly 8 percent of

[7] The denominator ($784.1 million) for this calculation was derived by taking the total non-AIDS funds allocated to investigator-initiated grants (research projects), all NIMH research centers and the proportion of the funds spent in R&D contracts that was for research projects only.)

the number of projects, but 12 percent of the funds, reflecting the large contract associated with the major trial in bipolar disorder (STEP-BD). In contrast, anxiety treatment trials accounted for nearly 15 percent of the number of projects in the portfolio, but 8 percent of the funds spent on RPG's and contracts in the DSIR clinical trials portfolio.

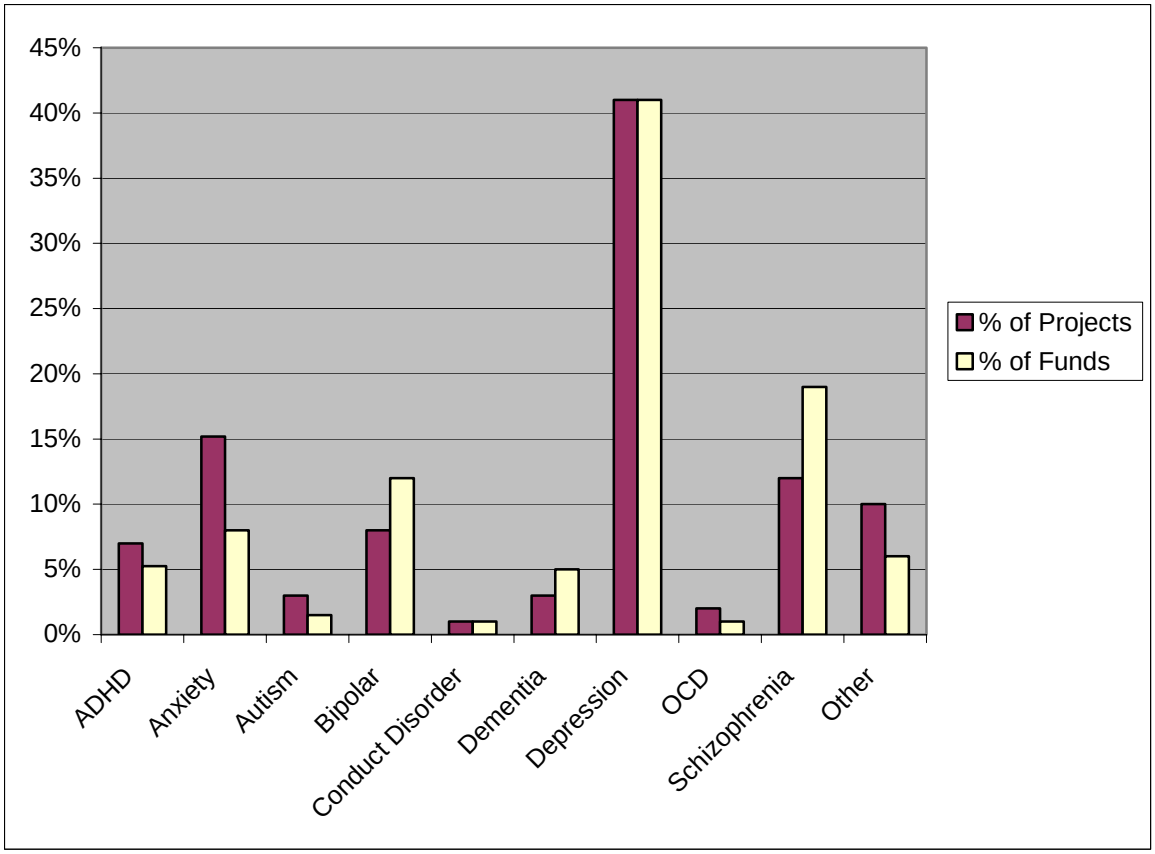
Table 1: The Number and Funding of RPG's and Contracts within the DSIR Clinical Treatment Trials Portfolio in FY 2003 by Disorder.

FY03 Treatment Portfolio by Disorder

	Number of RPG's & Contracts	Total $ in Millions
ADHD	14	4.7
Anxiety	30	8.8
Autism	6	2.0
Bipolar	16	13.1
Conduct Disorder	2	1.0
Dementia	6	4.7
Depression	84	43.7
OCD	4	1.2
Schizophrenia	24	20.3
Other[1]	21	6.0
Total	207	105.5

[1] Includes Personality Disorder, Sleep Disorders, Pathological Gambling, Insomnia, Somatization, and Traumatic Grief

Figure 2: Proportion of RPG's and Contracts within the DSIR FY03 Clinical Treatment Trials Portfolio by Disorder.



In looking at the portfolio by age group (Tables 2-4 and Figures 3-5), clinical treatment trials for adults and children in DSIR accounted for the bulk of the trials, representing 49 percent and 38 percent of the number of projects funded respectively, and 59 percent and 30 percent (Figure 3), respectively, in terms of dollars spent on these trials. Within the adult portfolio (Table 2, Figure 4), depression trials account for 51 percent of the projects funded, with 16 percent in anxiety and 14 percent in schizophrenia. Bipolar clinical treatment trials accounted for the smallest portion of the portfolio with 4 percent of the number of projects and 12 percent of the funds. In the child and adolescent segment of the DSIR portfolio (Table 3, Figure 5), ADHD, anxiety and depression together accounted for 59 percent of the projects and 61 percent of the funds disbursed. Autism, OCD, and schizophrenia together accounted for 19 percent of the projects and 17 percent of the funds, while conduct disorder received approximately 3 percent of the projects and funds.

In the part of the DSIR clinical treatment trials portfolio addressing geriatric populations (Table 4, Figure 6), depression, dementia and schizophrenia accounted for nearly 93 percent of the projects. Dementia, reflecting its growing importance as a mental health problem in the elderly, accounted for 41 percent of the funds.

Figure 3: Proportion of FY03 DSIR Clinical Treatment Trials RPG and Contracts by Age.

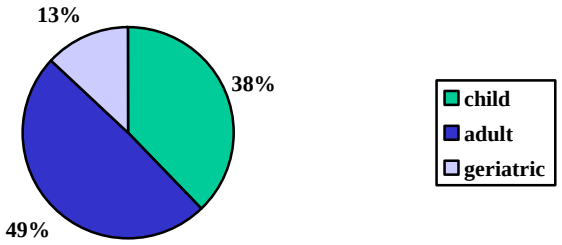


Table 2: RPG's and Contracts within the DSIR FY03 Adult Clinical Treatment Trials Portfolio by Disorder.

FY03 DSIR Adult Clinical Treatment Trials Portfolio

	Number of RPGs and Contracts	Total $ in Millions
Anxiety	16	3.9
Bipolar	4	7.7
Depression	52	29.9
Schizophrenia	14	15.9
Other[1]	16	5.0
Total	102	$62.4

[1] Includes Personality Disorder, Sleep Disorders, Pathological Gambling, Insomnia, Somatization, and Traumatic Grief

Figure 4: Proportion of RPG's and Contracts within the DSIR FY03 Adult Clinical Treatment Trials Portfolio by Disorder.

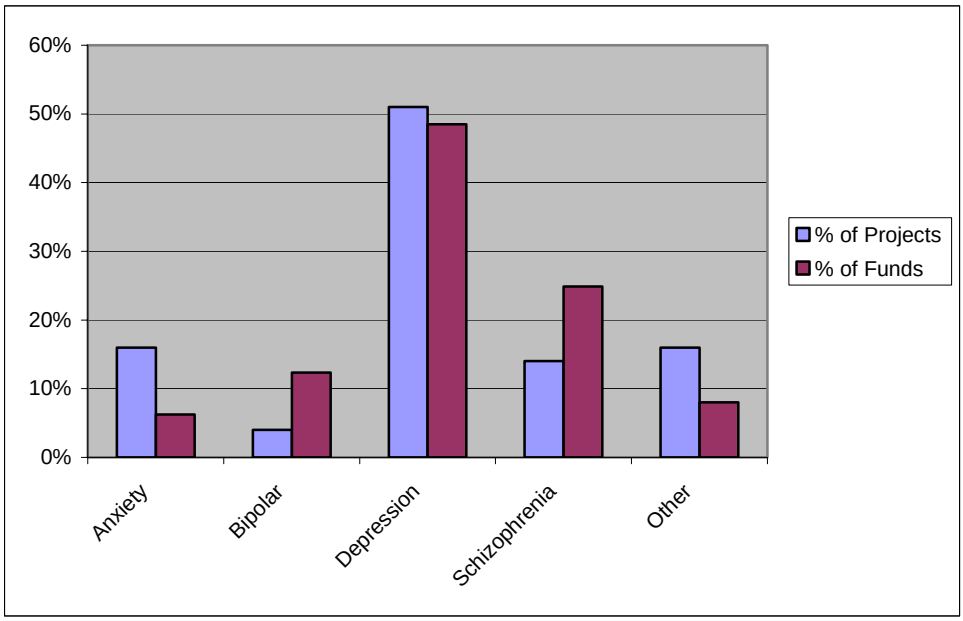


Table 3: RPG's and Contracts within the DSIR FY03 Child/Adolescent Clinical Treatment Trials Portfolio by Disorder.

FY03 DSIR Child and Adolescent Clinical Treatment Trials Portfolio

	Number of RPGs and Contracts	Total $ in Millions
ADHD	14	4.7
Anxiety	14	4.9
Autism	6	2.0
Bipolar	12	5.4
Conduct Disorder	2	1.0
Depression	18	9.7
OCD	4	1.2
Schizophrenia	5	2.2
Other[1]	3	0.5
Total	78	$31.6

[1] Includes eating disorders, body dysmorphic disorder, oppositional defiant disorder, and treatment of abused children

Figure 5: Proportion of RPG's and Contracts within the DSIR FY03 Child/Adolescent Clinical Treatment Trials Portfolio by Disorder.

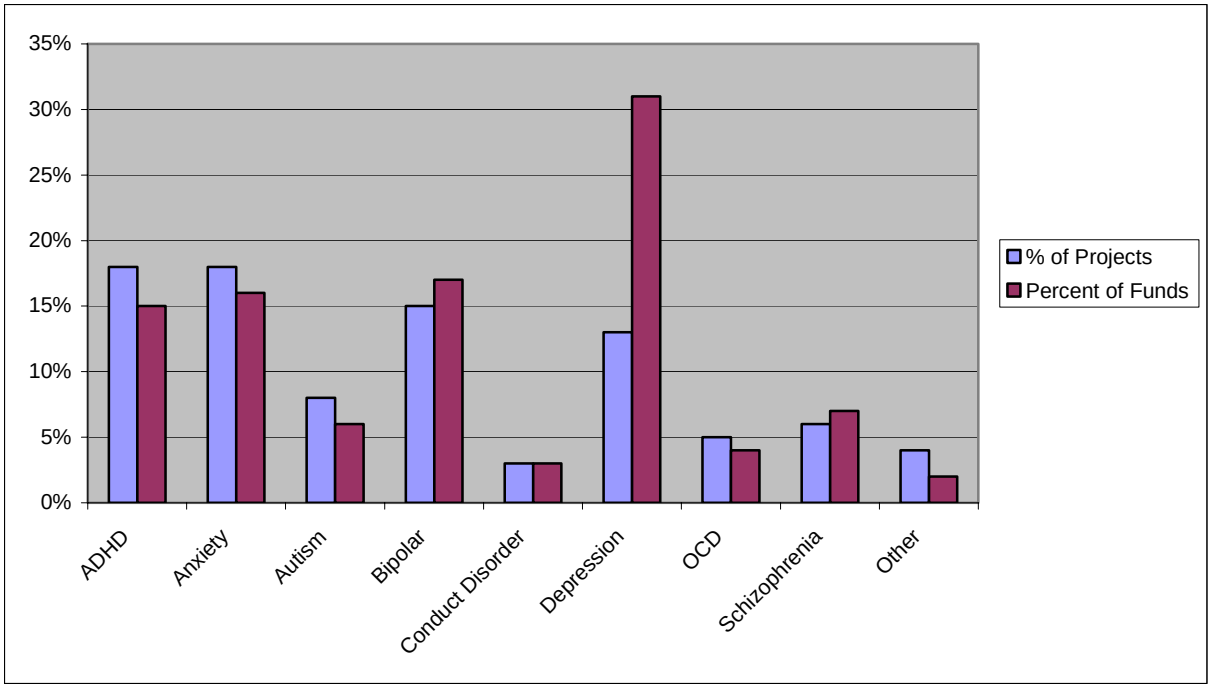


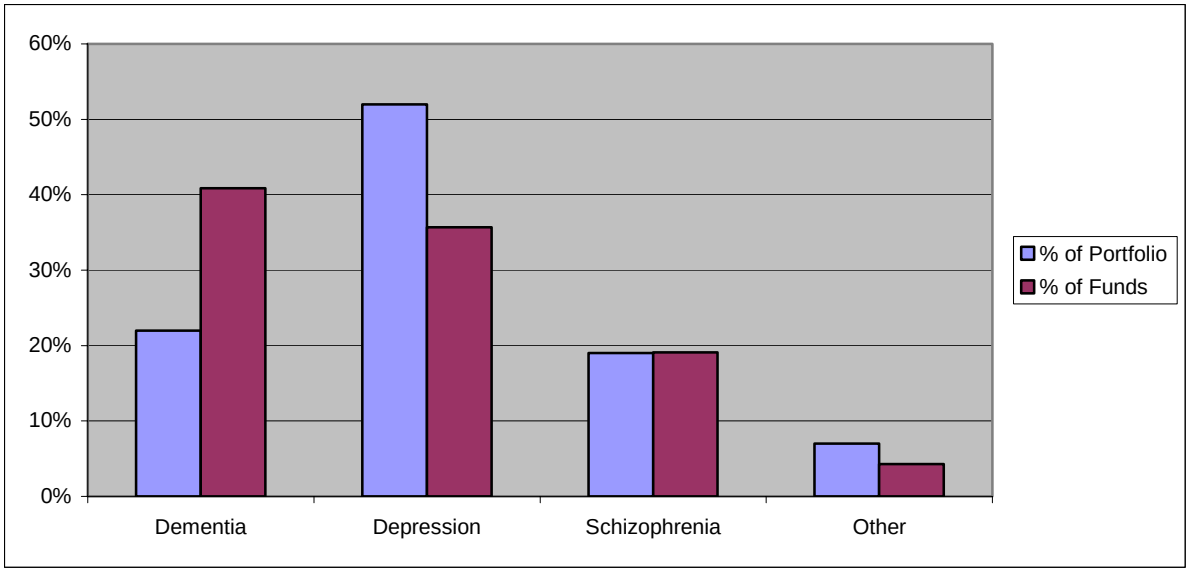
Table 4: RPG's and Contracts within the DSIR FY03 Geriatric Clinical Treatment Trials Portfolio by Disorder.

FY03 DSIR Geriatric Clinical Treatment Trials Portfolio

	Number of RPG's and Contracts	Total $ in Millions
Dementia	6	4.7
Depression	14	4.1
Schizophrenia	5	2.2
Other[1]	2	0.5
Total	27	$11.50

[1] Includes insomnia and long term effects of medications

Figure 6: Proportion of RPG's and Contracts within the DSIR FY03 Geriatric Clinical Treatment Trials Portfolio by Disorder .



A CLOSER LOOK WITHIN THE PORTFOLIO AREAS

Introduction

The Workgroup examined the NIMH clinical treatment program in the context of the public mental health needs of the Nation as reflected by current epidemiological data regarding disease burden and existing areas of scientific opportunity. In general, the Workgroup felt that the investigator-initiated research grant portfolio of DSIR reflected reasonable balance and proportional diversity with research studies ongoing in the range of mental disorders and age relevant populations using the various somatic, pharmacological and psychosocial treatment modalities that are currently or potentially indicated for the treatment of mental disorders and behavioral disturbances.

However, there were also areas where significant treatment questions appeared well-addressed (e.g. ECT), where more study is essential (e.g. treatment adherence, polypharmacy), and where the questions are no longer current (e.g., tardive dyskinesia). Further, too few studies were innovative and of potentially high impact on clinical practice. Similarly, a concern was expressed about the congruence of the research portfolio with the major questions confronted by mental health care providers on a daily basis. Notable exceptions to this concern were the contract-supported multi-site "practical trials" in bipolar disorder, major depression and schizophrenia which employed hybrid study designs, as well as the more recent multi-site intervention trials funded through the cooperative agreement mechanism that are focusing on clinical questions faced by community providers. The Workgroup thought these trials represented what should be an important segment of the NIMH treatment portfolio. The Workgroup endorsed recent efforts by DSIR staff to improve the public health relevance of treatment studies. The

NIMH should have a more active role in initiating studies of public health importance through the cooperative agreement or contract mechanism when investigator-initiated grants are not likely to address such issues.

Some members of the Workgroup expressed disappointment at the relatively small number of investigator-initiated trials that appeared to have immediate public health relevance and potential impact. The strongest trial designs to address questions of immediate public health significance often maximize external validity (generalizability) by adopting characteristics of effectiveness studies such as including study participants with diverse treatment histories and deleting randomization arms that include treatment approaches that would be unlikely to be used in routine practice settings. Several members of the group noted that such designs have great difficulty achieving fundable scores under the standard review process. NIMH has mounted such hybrid designs through the contract process but the review of investigator-initiated proposals proposing these types of designs remains challenging. The workgroup recommended that this be given particular attention for future discussion since disagreements among reviewers with respect to the merits of such designs can be a disincentive for investigators to propose trials of potential great public health significance using such designs.

It was also noted that, as the large trials funded under contract come to a close, the already underrepresented percentage of the portfolio emphasizing schizophrenia and bipolar disorder might be reduced even further. On the other hand, as these trials come to a close, there may be the opportunity to reallocate those funds to other studies of immediate practical significance to improve the balance of the portfolio. The NIMH has already begun to fund more studies that address important treatment issues faced by community providers and those living with mental illnesses. A large number of the clinical trials in the DSIR FY03 portfolio were started prior to this effort. Thus, these newer efforts are not reflected in the entire portfolio.

Based on its review, the Workgroup strongly endorsed the important role of the NIMH in fostering treatment research in mental disorders ranging from facilitating treatment development to evaluating the efficacy, safety and effectiveness of treatments, to provide an essential compliment to the extensive treatment research efforts of the pharmaceutical industry. The Workgroup also endorsed recent efforts by staff in the DSIR to improve the public health relevance of treatment studies. The NIMH should have an even more active role in initiating studies of public health importance through the cooperative agreement or contract mechanism when investigator-initiated grants are not likely to address such issues.

The Workgroup examined the FY2003 non-AIDS treatment portfolio by disorder, by age groups and by treatment mechanisms. As a result of these non-mutually exclusive crosscuts of the portfolio, there will be some overlap in the sections to follow in this chapter. The Workgroup also made several recommendations for specific subsets of the portfolio, and these are noted in the appropriate sections below.

Mood Disorders (Bipolar Disorder And Depression)

Depression is the most prevalent of all psychiatric disorders and the one with the largest number of studies in the NIMH treatment portfolio. Most treatment research in depression focuses on people with major depressive disorder (MDD). There are some studies of people who have depression comorbid with medical or psychiatric illnesses, treatment of depression in specific subtypes (chronic or minor depression) and grief in the recently bereaved.

The majority of the studies involve pharmacological therapy, while a smaller number focus on somatic treatments such as electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS). Psychotherapy is represented in slightly less than half of the trials and is often combined with medications A few studies examine the effects of psychotherapy in the absence of medication The types of psychotherapy being tested includes traditional cognitive behavior therapy (CBT) and interpersonal therapy (IPT), and others such as problem-solving training for depression in older patients with executive dysfunction and stress.

Given that efficacy of CBT and IPT has already been established for acute treatment of MDD, it is appropriate that these psychotherapies are now being evaluated in projects testing their usefulness in studies such as long-term prevention of recurrence and the identification of indices of differential response relative to medications. Dynamic psychotherapy is widely practiced but little studied; it is therefore encouraging that a placebo-controlled trial is underway to compare its efficacy with medication treatment. Similarly, it is encouraging to see a study investigating the efficacy of family therapy for depression.

Antidepressant medications (ADM), CBT and IPT have been shown to be efficacious in the treatment of acute depression, but nonetheless, important questions remain. Up to two-thirds of unselected outpatients will respond to any given intervention, but only about one-third will show full remission. Rates of response and remission are even lower in chronic patients and inpatient samples, especially when they have psychotic depression.

Even though there are existing interventions for depression that provide relief and have been proven efficacious, increasing the rates of full remission is required. Therefore, novel interventions are sorely needed, particularly those that draw on recent advances in basic research. Moreover, as effective as medications are, there is no evidence that they do anything to reduce risk of future depressive episodes if their use is discontinued. Given that depression tends to be a chronic recurrent disorder (10% of the general public account for 90% of the episodes) and that up to half of all patients discontinue medications against medical advice once they are better, it is clear that more needs to be done to develop interventions that have more enduring effects. Nonetheless, only a handful of the studies in the portfolio address the reduction of long-term risk and management.

Another concern is that little is known about the comparative effectiveness of different classes of antidepressants, nor about the usefulness of adjunctive pharmacy to enhance efficacy in patients with major depressive disorder (MDD). More work is needed to learn how to better treat patients who fail to respond to standard interventions. It was encouraging to see that this is a major focus of the current NIMH contract in depression (STAR*D).

Bipolar disorder remains strikingly understudied. Bipolar disorder is highly recurrent and can have a devastating effect on patients and families. As might be expected in a disorder that is so highly heritable and that so evidently involves biological dysregulation, all studies currently underway involve pharmacological interventions. Several psychosocial interventions have shown promise in recent studies as adjuncts to medication, including social rhythm, IPT and family focused therapy. Moreover, recent work suggests that CBT can also reduce distress and prevent recurrence in medicated patients. At present, the bulk of the Division's investment in bipolar disorder treatment research is represented by the STEP-BD study funded under a contract. This large (over 3,000 people), longitudinal investigation incorporates both pharmacological and psychotherapeutic interventions in the context of semi-naturalistic and smaller randomized trials. There is also a newly funded developing Interventions Center on Bipolar Disorder.

Among the funded projects specifically studying children and adolescents, the majority focuses on MDD, while a few study bipolar disorder. Most of the depression studies, but none of the bipolar studies, involve psychosocial interventions. The largest study in depression is the TADS study funded under a contract. It is a multi-site study designed to determine whether pharmacotherapy alone, psychotherapy alone or a combination of the two are better than placebo in adolescents. Another study is focusing on whether switching within or across medication classes or augmenting with CBT will enhance response in adolescents who have been refractory to medication treatment. Other studies are testing whether the addition of parent training can enhance the efficacy of CBT in the treatment of preadolescent girls diagnosed with depression and whether a multi-family psycho-education group therapy program (MFPG) can reduce distress and enhance family functioning.

Overall, depression appears to be well represented in the existing portfolio for adult and geriatric populations, as is appropriate for the most prevalent of the major psychiatric disorders, and underrepresented in studies of children and adolescents (except for the TADS trial) Bipolar disorder is clearly underrepresented in the investigator-initiated grant portfolio. The bulk of the studies with adult and geriatric populations focus on medications or somatic treatments and this is invariably the case among studies of bipolar populations at any age. Most of the studies still focus on acute treatment and virtually none look for enduring effects. In fact, recent psychosocial innovations that show promise are notably underrepresented in the portfolio and, with the exception of STEP-BD, none are currently being tested with respect to bipolar disorder. Studies focused on testing novel therapeutic approaches and combination therapies are underrepresented in the current portfolio, as are pharmacogenomics studies.

Schizophrenia

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) contract is the largest effort in schizophrenia treatment research funded by the Division. The is a multi-site, randomized clinical trial examining long term, symptomatic and functional outcomes designed to answer the basic question about differential effectiveness of the new atypical anti-psychotics. Additionally, two Intervention Research Centers deal exclusively with the treatment of schizophrenia, while another Center devoted to geriatric psychiatry has schizophrenia as one of its major foci. Other treatment studies in the Division target first episode schizophrenia, management of comorbid drug abuse in people with schizophrenia, treatment of negative symptoms, and managing treatment refractory patients who do not respond to clozapine. NIMH-funded research on schizophrenia is notable for the effective manner in which the projects complement one another and mesh with industry-sponsored research.

The schizophrenia treatment portfolio addresses most major first-order questions about the treatment of schizophrenia, but more attention should be paid to psychosocial interventions, and research needs to move beyond treatment of symptoms, towards improvement in functional status and management of illness. One of the biggest issues facing the schizophrenia treatment research portfolio is what will happen after CATIE ends. The successful completion of the CATIE trials is likely to raise as many questions as it answers, even as completion of the contract frees a great deal of financial and human capital. Whether these resources will continue to be invested in schizophrenia treatment research remains to be seen.

Workgroup members expressed a strong interest in seeing more partnerships between NIMH and other agencies like SAMHSA as potential co-funders of research in this area. In addition, several members emphasized the need to make connections with those in the States who are responsible for delivering care to people with this illness. Almost all expressed an interest in studies that would address the use of polypharmacy and how to intervene in those who have co-morbid disorders. A strong emphasis was placed on the need for the NIMH to interface with the public mental health sector in planning and conducting clinical trials in people living in the community with this illness.

Anxiety Disorders

Overall, research on Anxiety Disorders is under-represented in the portfolio given that these disorders are among the most common psychiatric conditions in the community. Several decades of industry-sponsored studies, as well as NIMH-funded research, have produced a group of proven, efficacious medication and psychosocial treatments for these disorders. Still, there are many questions that remain unanswered, and there is a pressing need for innovation, especially in the areas of translational research and dissemination research. Anxiety disorders lend themselves particularly well to translational research since fear is one of the most studied neurobiological phenomena. Recent findings related to biological and psychological processes that underlie fear conditioning could be translated to improving treatment of anxiety disorders. These findings could provide the basis for innovative treatment applications. There is a pressing need for innovative, large-

scale, multi-site studies addressing issues such as those related to therapist and patient behaviors, diversity issues in acceptance and response to treatment, the importance of comorbidity, and cost effectiveness of interventions. In addition, there is a need for studies that explore ways to achieve full remission in the anxiety disorders.

Research addressing populations with high degrees of comorbidity is particularly important. Neither mood nor anxiety disorders exist frequently in pure form, and there is a need for studies that specifically acknowledge this clinical reality. Such studies need to target optimal resolution of symptoms of all co-occurring disorders, as well as long-term maintenance strategies. In addition to their role in relieving distress from existing conditions, such studies would inform efforts to prevent complications of stressful life experience that are more likely to occur in someone with a concurrent mood or anxiety disorder at the time of the stressor.

The current portfolio's studies in Panic Disorder represent appropriate new directions for research in this area, with each contributing something important and unique. In that sense, this disorder is fairly well represented in the current portfolio. However, few studies are conducted in community samples.

The portfolio of studies in Post-Traumatic Stress Disorder (PTSD) also represents new and useful directions in this area, and each is a reasonable contribution. There is, however, a notable absence of pharmacologic and neurobiological studies. Though PTSD is relatively well represented in the portfolio, and studies will undoubtedly provide the field with useful information, the current portfolio does not include exciting translational research, and only one relatively small study targets a community population. There is also a need for a large multi-site study in this important area.

The other anxiety disorders are greatly under-represented in the portfolio. There is only a single study in Social Phobia. There is minimal research on Obsessive-Compulsive Disorder (OCD). There are no studies of Generalized Anxiety Disorder (GAD). It is worth noting that GAD is the one condition where CBT has not been clearly demonstrated to be efficacious.

Personality Disorders, Sleep Disorders, And Others

The size of the investigator-initiated grant portfolio in disorders other than Mood Disorders, Schizophrenia and Anxiety Disorders is very small. Thus, disorders that did not fall within the three largest components of the portfolio are discussed here. The portfolio includes a few studies of eating disorders, pathological gambling, borderline personality disorder, insomnia, and somatization, but not at the level needed given that several of these areas are prevalent, disabling and potentially life-threatening disorders. Personality disorders and somatization are highly prevalent conditions for which there are virtually no proven efficacious treatments, and the portfolio must include more research in this area. Bereavement-related conditions are also highly prevalent and greatly debilitating, yet intervention research in this area is poorly represented in the portfolio and needs to be increased.

Eating disorders are somewhat better represented than the other illnesses in this category, but the preponderance of studies are on bulimia. Studies are needed on anorexia nervosa, the most intractable and potentially lethal eating disorder. Relative to the other disorders discussed here, studies of pathological gambling are the most highly represented in the portfolio. In contrast, there is a lack of research in important public health and clinical problems such as delirium, sleep disturbance and co-morbid substance abuse problems. This may stem from the fact that investigator-initiated studies tend to focus on disorders as opposed to focusing on clusters of symptoms and how to intervene in those symptoms.

Child And Adolescent

The NIMH Child Treatment portfolio reflects the considerable efforts made to stimulate interest and develop studies in pediatric populations with mental disorders. Most of the studies are in the areas of depression, anxiety disorders and attention deficit hyperactivity disorder (ADHD). The remainder of studies is in bipolar disorder, autism, schizophrenia, conduct disorder and others, including eating disorders. The primary questions being addressed by these studies include:

- What are the efficacy and effectiveness of the most commonly used treatments?
- What is the safety of the most commonly used treatments?
- Which interventions work for which children?
- What is the impact of context and co-morbidity?
- How can we address treatment non-response?
- What is the long-term impact of early treatment interventions on psychopathology?

One of the main strengths of the current investigator-initiated treatment grant portfolio is its emphasis on the treatment of children with ADHD and adolescents with anxiety disorders and depression. Other strengths include a close interface among treatment programs and an infrastructure for conducting multi-site clinical trials. There are notable weaknesses, however, particularly in treatment studies of such important public health problems as bipolar disorder, prepubertal depression, eating disorders and conduct disorder. More clinical trials testing psychopharmacological interventions are needed. In addition, the Workgroup identified a necessity for more trials focused on interventions at an earlier stage of the illness, that is, for those identified early or those “at risk.” The current portfolio includes few effectiveness studies and treatment studies that are limited largely to short-term outcomes. In addition, the small pool of researchers with the interest and expertise to study treatments for children and adolescents are engaged in current studies, making it difficult to launch new studies.

In the area of autism, the infrastructure for multi-site clinical trials of pharmacology, psychosocial, and combined treatments is reasonably well developed through the RUPP[8] mechanism and participation in multi-institute initiatives. NIMH has recently launched

[8] The NIMH funded Research Units in Pediatric Psychopharmacology (RUPP) to provide infrastructure support for multi-site treatment trials of new psychopharmacology and psychotherapy interventions in children and adolescents.

several new projects (STAART network)[9] that include new intervention projects, two of which are multi-site efficacy trials. In addition, the Institute has made creative use of SBIR contract mechanisms to explore the feasibility of adapting existing interventions (e.g., social skills training, peer training) to autism, and for web-based mechanisms to disseminate empirically-based information to practitioners.

Limitations of the autism program include a lack of innovative developments in psychosocial interventions and a dearth of attempts to adapt evidence-based treatments for use with autistic individuals, with few interventions directed toward the core autism features. There are also few definitive studies on the efficacy of many psychosocial treatments commonly used and few studies that address individualizing treatment in this heterogeneous population. There are no current studies addressing contextual variables, or long-term outcomes. Finally, there are a limited number of investigators addressing autism treatments. To remedy these shortcomings, the Workgroup recommends that the NIMH should encourage development of innovative treatment approaches, expand psychosocial research in autism, and capitalize on multi-institute collaborations that foster multi-disciplinary research.

Geriatrics

The grants that specifically address geriatric populations cover predominantly the major psychiatric disorders (e.g., depression, dementia, and psychosis) with a significant burden, that is, disorders that have a relatively high prevalence, high level of severity, likelihood of long-term morbidity and mortality, and great public health significance. The research questions under study are important and relevant.[10] For example, there are studies of treatment for agitation in dementia and improving medication adherence in schizophrenia that have high scientific, clinical, and public health importance. These studies are likely to provide information relevant to clinical practice. In addition, the work being funded is not currently supported by the private or public sectors, and it is not likely to receive the necessary private sector funding in the near future.

A number of the studies in the NIMH geriatrics portfolio are highly innovative. For example, one multi-site study examines the neuroanatomy of treatment resistance in late-life major depression, while another is evaluating the augmentation of pharmacotherapy in geriatric depression with therapeutic sleep deprivation. The portfolio includes a study that assesses the effectiveness of exercise training in reducing depression, and yet another study that tests the usefulness of a functional skills training paradigm for older people with schizophrenia.

There are, however, some important limitations to the current portfolio. For example, there is little attention paid to anxiety, one of the most common psychiatric disorders in the elderly. There are no treatment studies of delirium, bipolar disorder, co-occurring

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[9] Studies to Advance Autism Research and Treatment; These are co-funded by NIMH, NINDS, NICHD, NIDCD, and NIEHS.

[10] See NAMHC's "Mental Health for a Lifetime: Research on the Mental Health Needs of Older Americans" for a full discussion at http://www.nimh.nih.gov/council/agingreport.cfm.

alcohol and substance use disorders, or personality disorders among the elderly. Additionally, the number of studies of psychosocial interventions in older patients is very small. Given the limitations of pharmacotherapy in late life, there is a critical need to develop and support additional investigations of psychosocial treatment modalities in this age group.

There is a need to evaluate the performance of proven treatments in community populations using practical measures of outcome. Few, if any, studies focus on underserved populations. As the population of elderly ethnic/racial groups is expected to rise dramatically over the next several decades, treatment trials need to do more than merely include “adequate numbers” of racially diverse groups.

In discussions about the unmet and future needs for research not addressed in the current portfolio, the Workgroup noted that an important consideration is that as the population of elderly mentally ill persons is expected to more than double in just 30 years, there is a critical need for a considerable increase in funded research in this area. Findings from younger adults cannot be extrapolated to the geriatric population any more than they can be to children. The Workgroup recommends particular emphasis on treatment studies of disorders that are poorly represented in the current portfolio; studies of psychosocial treatments, and treatment trials focused toward specific racial/ethnic groups of older patients.

Methodological innovations will be needed to conduct effectiveness studies in high-risk elderly patients. Examples include creative ways to conduct randomized controlled trials involving some treatments that may not be preferred by patients' own clinicians, more sophisticated statistical analyses than the ones used traditionally, and processes to ensure adequate comprehension of complex consent forms in cognitively impaired patients.

In sum, the current portfolio in mental health geriatrics is excellent in terms of quality of the work being done. However, the Workgroup was concerned about the areas that are not covered, especially in view of the rapidly growing population of elderly mentally ill Americans. The Workgroup suggested that NIMH should find ways to coordinate larger trials on comorbid disorders with the National Institute on Aging and the National Institute of Neurological Disorders and Stroke.

Psychosocial Interventions

In the adult and geriatric portfolio, psychosocial interventions are represented in just under half the portfolio, with additional studies focused on psychosocial rehabilitation in people with dementia or schizophrenia. In contrast, a majority of the portfolio deals with medication treatment, with a few studies examining ECT or other somatic interventions. The cognitive behavior therapies (CBT) are the most frequently represented psychosocial modality, though there are trials featuring behavior therapy (BT), interpersonal psychotherapy (IPT), dynamic therapy and family therapy. The CBT studies are distributed across a range of disorders, with the majority focused evenly on depression or anxiety disorders, whereas the BT studies are concentrated in the anxiety disorders and borderline personality disorder. IPT, dynamic psychotherapy, and family therapy are

found only in depression studies. Over two-thirds of these studies focus on acute treatment, often with naturalistic follow-ups, although there are trials that focus on continuation or maintenance treatments. Only one study in the portfolio would permit the detection of enduring effects, despite the fact that such effects represent the primary potential advantage for psychotherapy over medications and have been found in most comparative studies in the non-psychotic disorders. Such designs typically treat patients with either drugs or psychotherapy and then follow responders over some extended period after treatment termination.

The picture is somewhat different for the child and adolescent disorders. Psychosocial interventions are represented in the large majority of studies, whereas medications are represented in less than half the studies (some studies include both types of intervention). CBT is again the most frequently tested intervention, but is followed closely by BT and family therapy. The anxiety disorders account for the bulk of the psychotherapy trials, though the portfolio also includes a significant number of studies using BT in attention deficit disorder. The remaining studies are scattered across the other disorders; the only intervention that appears in more than a single study with a given disorder is an eclectic multi-system therapy for conduct disorder. Only a few of the existing studies examine lasting or enduring effects. This is somewhat surprising given that many of the disorders studied are likely to extend into adulthood.

On the whole, the Workgroup noted that the NIMH portfolio for adult and geriatric populations appears to be weighted toward the medication and somatic interventions, whereas the child and adolescent portfolio appears to show the opposite pattern. CBT dwarfs the other psychosocial interventions in the adult portfolio, while it is more nearly matched by BT and family therapy for children and adolescents. Interpersonal and dynamic therapies remain little studied. The bulk of the studies across all age groups focus on acute interventions; studies of continuation and maintenance treatment are only rarely found in adult and geriatric samples and studies capable of detecting enduring effects are virtually non-existent.

The Workgroup noted that other weaknesses include a lack of focus on complex cases/issues, including comorbidity, treatment resistance, partial response, relapse, attrition, and cognitive issues in geriatric patients. The portfolio contains few studies on the use of psychosocial therapy in severe or chronic mental illness. The Workgroup noted that there is a lack of attention paid to cost-effectiveness and that little will be learned from these studies in terms of why therapies work or how to streamline psychotherapy packages.

A strength of the current portfolio is that it contains a large base of efficacy studies, with good coverage of depression and anxiety disorders, in general, and involving women in particular. In addition, there are a significant number of small grants developing new interventions or adapting existing ones for new uses, and the use of SBIR grants to disseminate psychosocial interventions is innovative. The Workgroup also noted that the portfolio reflects some progress in using new treatment modalities, including computers and telehealth systems. The portfolio also encompasses a range of service settings, including community clinics and child welfare, and has established a growing

infrastructure, primarily through center grants to support the translation of efficacious treatments to community settings such as primary care and schools.

The Workgroup was encouraged by the funding of larger trials such as STAR*D[11] that are testing psychosocial treatments in community populations and looking for enduring effects. But, to further strengthen the portfolio, the Workgroup recommends that NIMH should do more to encourage the development of new psychosocial treatments based on discoveries in basic science and to increase the public health relevance of the studies it funds. In addition, NIMH needs to fund more work adapting therapies for use and study in typical care settings, particularly geriatric settings such as nursing homes, as well as a need to test psychotherapies in racial/ethnic populations. There is also a need to focus more research on complex cases and to orient research toward helping patients to achieve more complete and durable recoveries as outcomes. There should also be an effort to foster linkages between general adult and geriatric fields in order to broaden age ranges included in studies and to design more studies making age comparisons. Computer-based therapies and other novel therapeutic approaches are also underrepresented in the current portfolio.

In terms of methodological issues, the Workgroup noted that there is a need to facilitate the transition of small grants into subsequent larger scale studies, and to encourage training and career development in order to broaden the base of investigators. There is also a need to support development and adaptation of new methods and a need for new methods for obtaining cost-effectiveness information.

Psychopharmacology

The strength of the current portfolio in psychopharmacology is the funding of multi-site trials (including through the contract mechanism) in depression, bipolar disorder, anxiety disorders, autism, and schizophrenia. The most notable weakness is the lack of studies testing psychopharmacological treatments in OCD, eating disorders, and prepubertal depression. There are also few studies of treatments of comorbid disorders or on the use of combinations of medications. In addition, most studies in the portfolio focus only on short-term outcomes and symptom resolution.

The Workgroup recommends that priorities for improving the psychopharmacology portfolio should include funding more trials of early treatment of severe mental disorders (e.g., bipolar disorder, major depression and schizophrenia), treatment resistant depression, anorexia nervosa, autism, and treatment resistant OCD. The Workgroup recommended that NIMH should also develop methodology to study long-term safety of medications, medications that are commonly prescribed to children without adequate supporting data on their safety and efficacy, and medication combinations.

In the area of trials for evaluating combinations of psychotherapy and pharmacotherapy, the Workgroup noted that the portfolio is strong in comparative efficacy studies across a relatively broad range of disorders, including major depression, schizophrenia, adult

[11] Sequenced Treatment Alternatives to Relieve Depression (STAR*D)

bipolar disorder, various anxiety disorders, ADHD, and bulimia. Compared to earlier research, these studies feature fewer exclusions to participation, making the portfolio more representative of community populations. The portfolio also reflects a growing emphasis on flexible, algorithmic, representative pharmacotherapy, as well as a growing attention to maintenance treatment, sequencing issues, and longer-term outcomes. Outcome assessments have also been broadened to include function, quality of life, service utilization and costs considerations.

Weaknesses in the existing portfolio include relatively little depth in terms of studies in any single disorder, and an insufficient number of projects focusing on difficult-to-treat cases, including treatment failure or resistance (except STAR*D), partial response, and residual symptoms. The portfolio is particularly weak in the area of bipolar disorder (other than the STEP-BD trial), and the Workgroup also noted that there is minimal work focused on optimizing composite approaches to comorbid conditions. Other weaknesses in the portfolio include a limited interface between treatment and services research, and minimal inclusion of policy relevant outcomes such as cost effectiveness.

Somatic Treatments

The Workgroup noted that the somatic treatments portfolio included comprehensive coverage of electroconvulsive therapy (ECT), both for acute and maintenance treatment. In fact, this area of research appears to be well covered regarding novel approaches to delivering ECT that optimizes the risk/benefit of this treatment. The portfolio also addresses the efficacy of repetitive transcranial magnetic stimulation (rTMS), and provides support for early studies of a range of novel somatic treatments, including deep brain stimulation (DBS).

One of the main weaknesses in the current portfolio is that it supports few studies comparing somatic with standard pharmacologic or psychotherapeutic interventions. The Workgroup also noted that there is little support for studies on combined use of medications and somatic treatments, and no support for somatic treatments of comorbid disorders. The portfolio also includes few studies of somatic treatments in disorders other than depressive spectrum disorders

The Workgroup recommends that NIMH priorities in the somatic treatments portfolio should include the development of methodologies for random-assignment comparison trials of somatic treatments and pharmacotherapies The workgroup also encourages continuation and maintenance trials of other promising new somatic treatments.

CAREER DEVELOPMENT AND TRAINING AWARDS IN CLINICAL TRIALS RESEARCH

The Workgroup also requested data on the number of career development and research training that were given to investigators interested in pursuing treatment research. Of the 456 career awards in non-AIDS areas, 74 or 16.2 percent of NIMH career awards were for investigators pursuing clinical treatment research. The percentage of pre-doctoral and post-doctoral training positions and individual fellowship awards is smaller, with 87 of the 1,280 positions or 6.8 percent of the total NIMH number of trainees in non-AIDS areas involved in clinical treatment research training.

Given the importance of this area and the need to bring more clinical people into research as emphasized by the NIH Roadmap, the Workgroup was concerned about the small number of such awards. This is of particular concern since the NIMH is the only Institute that would support training of clinical researchers in mental health. The Workgroup decided that it is important for the NIMH to expand its efforts to increase the number of investigators in clinical treatment research. This is particularly important in those areas where there are already small numbers of investigators and a growing need for more treatment research (i.e., child and geriatrics fields).

CHAPTER IV
OPERATIONAL ISSUES AND APPROACHES FOR STRENGTHENING CLINCIAL TRIALS

It was recognized by the Workgroup that treatment research is inherently different from other forms of research funded by the NIMH in terms of the scale and cost of the projects required to address key issues affecting mental health. The group noted that the evolution of the range of funding mechanisms including individual and collaborative RO1's, UO1's, R34's, Centers and Contracts, has recapitulated a developmental course successfully taken by other NIH Institutes, including the National Cancer Institute and National Heart, Lung and Blood Institute. However, with increasing complexity and scope comes greater potential for problems. The Workgroup therefore considered how well these costly investments were progressing and how to ensure their success.

OPERATIONAL PERFORMANCE: RECRUITMENT

The Workgroup was interested in evaluating the performance of the NIMH extramural clinical trials in terms of meeting proposed recruitment goals. Meeting recruitment goals is essential since sufficient sample size is an important factor in meaningfully assessing critical treatment questions. To get a comparative look across trials it was decided to focus only on grants that were in their last project year (i.e., the point at which recruitment should have finished) or those that had a no-cost extension during FY03. The projected recruitment targets for each grant were compared to their actual recruitment, and grants were considered successful if they met or exceeded 80% of their target recruitment goal. It should be emphasized that 80% is actually a generous allowance as most studies must achieve 100% of their recruitment goal in order to have enough subjects to permit informative analyses of the original study questions.

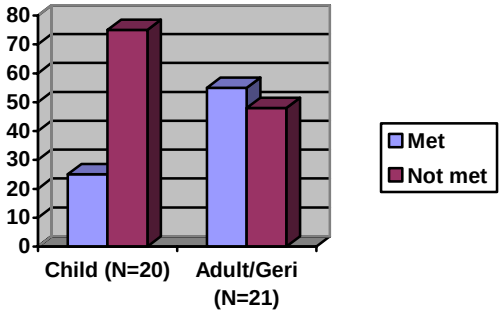
Overall Recruitment

As Figure 7 shows, recruitment failure is a shortcoming affecting investigator-initiated treatment trials in the NIMH portfolio. Because the failure rate for the trials in the adult and geriatric areas differed so significantly from that of the child trials, these are reported separately. In the adult and geriatric trials, 48 percent did not meet the target recruitment goal, while in the child area, 75 percent failed to meet the target recruitment goal by the end point of the study. Clearly, too many studies failed to meet their overall recruitment goals.

In some cases, recruitment goals may be achieved ultimately through additional time allowed in no-cost extensions or additional funding periods. Because these data were based on investigator-initiated grants that had their last year of support in FY03, the findings here do not reflect more recent efforts undertaken by the Division during the past several years to improve recruitment. Such efforts have included converting the large multi-site collaborative investigator-initiated grants into cooperative agreements. This gives the NIMH more oversight on the study and allows staff to assist investigators in recruitment initiatives. Grants funded now under cooperative agreements and the current large trials funded under the contract mechanism have performed much better in

obtaining their projected recruitment goals than investigator-initiated grants not funded under these mechanisms. In fact, all the large trials funded under a contract mechanism (except STEP-BD which is still in progress) have achieved their overall recruitment goals.

Figure 7: Recruitment goals for clinical trial grants in DSIR: percent achieving ≥80% of goal by last year of project.



Recruitment of Historically Under-represented Populations

In addition, the Workgroup looked at the success of treatment grants to achieve their recruitment goals for historically under-represented populations. The Workgroup looked across all studies in process and was concerned that such recruitment appeared low in select studies, particularly in single site studies and in some of the sites in multi-site studies. The Workgroup was interested in seeing if minority recruitment was on par with overall recruitment or if it was different. As in the section on overall recruitment discussed above, success was defined as achieving 80% of the targeted sample goal.

Figure 8: Recruitment goals for underserved populations in DSIR clinical trial grants: percent achieving ≥ 80% of historically under-represented population goal.

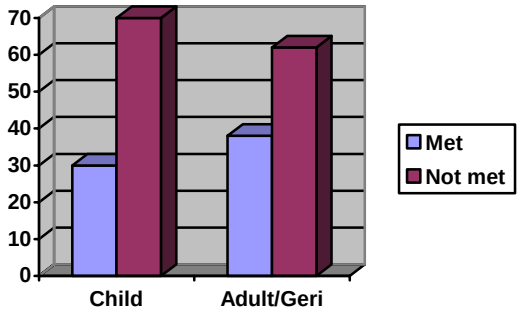


Figure 8 shows that efforts to recruit such populations were problematic. Over 60 percent of the adult and geriatric trials failed to meet at least 80 percent of the initial enrollment goals, while 70 percent of those involving children and adolescents did not succeed in meeting stated recruitment goals for these populations.

It is important to note that the poor success here could be affected by the poor success in general recruitment (see Figure 7). If general recruitment is low, then the recruitment of any specific population might also be low. Thus, to make comparisons that account for overall recruitment success across grants, the recruitment of under-represented populations could be adjusted to account for poor general recruitment in a grant. To do so, one could determine if a study at least met the "proportion" of such populations that were initially projected at the start of the study. Applying this method to the same grants used for Figure 7 and 8, the "success" in recruiting historically under-represented populations would look different. Eighty percent of multi-site trials in the adult area were able to attain the expected proportion while 69 percent of the single site grants achieved their proportion of these populations. In those grants involving children, only one of the three multi-site projects had a final recruitment proportion of underserved children that met the targeted proportion, while 65 percent of the single-site projects in children met this goal. However, even with such adjustments recruitment of historically under-represented populations continues to be a problem in investigator-initiated grants. In contrast to these figures on investigator-initiated grants are several of the largest studies, such as some of the multi-site research projects funded as contracts. Most of these are exceeding their targets for recruitment of ethnic and racial minorities and women.

The Workgroup also considered the percentage of each underserved racial or ethnic group in the final numbers of those recruited by the same grants noted above (i.e., those in their final year of funding in FY03). The purpose was to determine if particular groups are under-represented. In the adult trials funded by the grant mechanism, about 26 percent of all those recruited were from an underserved population. People who identified themselves as black made up 18 percent of those recruited, 1 percent were Asian, and 2 percent were identified as "other." Hispanics accounted for 4 percent of all those

recruited. In child trials funded by the grant mechanism, 40 percent of all those recruited were from an historically under-represented racial or ethnic population. Children who identified themselves as black accounted for 26 percent of those recruited, 1 percent were Asian, and 4 percent were identified as "other." Hispanics accounted for 10 percent of those recruited. American Indians and Pacific Islanders made up less than 1 percent of those people recruited for participation in both the adult and child grants. Once again, these figures represent only the proportion of people recruited but do not indicate whether the total numbers are adequate.

The Workgroup also recognized an additional issue related to recruitment of specific populations. The data regarding success of recruitment do not take into consideration whether the originally **projected target** number for historically under-represented populations was appropriate. An investigator could achieve 100% of a target number, but if the target number were inappropriately low, representation would still be inadequate. In short, overall recruitment needs to be bolstered, with concomitant attention to recruitment of historically under-represented populations as a specific additional issue. The Workgroup recognized that involvement of historically under-represented populations in clinical research is an issue that faces all clinical research across NIH and encouraged the NIMH to serve as a model for implementing efforts to improve such involvement.

LESSONS LEARNED: NHANCING RECRUITMENT IN CLINICAL TRIALS

The number of large clinical trials funded by DSIR, especially clinical trials funded through Cooperative Agreements, has increased over the past several years. Large clinical trials are also supported through other funding mechanisms such as collaborative R01s and research contracts. Unfortunately, as documented above, clinical trials are often plagued by low subject enrollment.

There are a myriad of issues affecting enrollment, including study design, site selection, and diversity of the sample. However, regardless of their ability to enroll subjects, there are operational problems that exist across these trials that may affect their quality and hence their ability to address the important research questions they pose.

This overview will propose solutions to address these issues in the planning, review and oversight process. Although the issues are applicable to all types of clinical trials, the solutions proposed here are particularly important for the larger clinical trials. This includes any application requesting a budget of at least $500,000 in direct costs in any one year of funding.

Study Design

One of the basic justifications for a multi-site clinical trial is that the issue being studied requires a large and diverse sample size that is beyond what one site can achieve alone. However, increasing the number of sites included in the trials is not often sufficient to enroll the required number of participants because, for a variety of reasons, many sites fail to enroll their target sample sizes, leaving the total sample inadequate.

Multi-site trials may involve complex designs with narrow inclusion criteria, resulting in many exclusions at screening. For example, in a recent pediatric study, 57% of those pre-screened did not meet criteria; while in another 66% of the subjects who were pre-screened did not meet the inclusion criteria. Studies may also require screening people at successive stages, each requiring significant clinician time. The result can be a large expenditure of resources on many subjects who never enter a study. However, since the rationale for a large study is almost always related to studying the relevance of a treatment for a "real life" community population, it is often inappropriate to have many exclusion criteria or to have very narrow inclusion criteria. At the same time, it is important that the study is designed to answer the appropriate questions.

Another factor impacting enrollment is that some trials attempt to enroll populations that are reluctant to participate in research. For example, one study recruited pre-school children with ADHD into a trial where they will receive medication. Diagnosing pre-school children with ADHD is a controversial topic; medicating them is even more controversial. Being confident in the diagnosis involved screening at successive points, but maintaining parental interest in the child's participation in the trial proved to be problematic. While it is likely that these kinds of problems will occur in studies addressing the usefulness of a treatment for the larger community, study questions should be rethought rather than pushing ahead. Complex designs are often needed to answer important questions that cannot be addressed with simpler designs, but pilot studies or previous experience may be required to design an achievable plan for recruitment.

The necessity to schedule study assessments around subjects' school and work schedules may not be properly accounted for when outlining study operations. In addition, in trials in which treatment is not provided free of charge, there may be insurance reimbursement issues that deter subjects from enrolling. That is, health insurance may not cover treatment-related visits that exceed the insurance plan's limits but which may be required as part of the study design. Also, participants may not see study participation as a worthwhile expenditure of limited health plan visits.

Recruitment/Retention Strategy

Too often, studies depend on a single recruitment strategy for recruiting participants. Estimates of recruitment potential tend to be overly optimistic and not based on actual prior experience. There is a propensity to use advertising or similar approaches that mimic those taken by pharmaceutical companies and contract research organizations for short-term studies of drug efficacy. Even when multiple approaches to recruitment are taken, they may not be planned carefully and, as the slow rate of enrollment becomes obvious, the study may scramble to initiate alternative strategies that can be very expensive (such as initiating new sites), and unsuccessful. Investigators also often fail to consider the importance of having a racially and ethnically diverse participant pool during the development of a recruitment plan, and they may not plan for differences in language, cultural factors and the potential for community engagement that may impact recruitment. If plans are not made to engage diverse community populations from the start, the study is likely to fail in efforts to recruit diverse participants.

Experience in retention of participants in longer duration effectiveness studies is limited in mental health research, but is quite important. Studies must balance rapid recruitment pressures with the potential for premature dropout of marginally committed patients. Poor retention of participants throughout the period of a study can create problems for statistical power and analysis. However, it is important to keep in mind that while retention is a problem for evaluating efficacy, it is a meaningful outcome for effectiveness studies. There is a need for all studies to separate assessment and treatment protocols such that a participant can drop out of treatment and still be strongly supported and encouraged to remain in the assessment protocol.

The Workgroup discussed ways in which fiscal incentives might be better aligned so that funding was put at risk by poor performance and enhanced by good performance. Such a policy would incentivize performance. Moreover, fiscal incentives could enhance gender and racial/ethnic group proportions. The Workgroup endorsed efforts by the DSIR staff to improve recruitment through consultation with investigators and assuming a more direct collaborative role through the cooperative agreement and contract mechanisms. More involvement by NIMH staff has appeared to help performance of many studies

Site Selection

In the planning and design process, once the total sample size requirement has been determined, the number of participants expected to be enrolled at each site determines the number of total sites needed. As part of the application submission, applicant sites estimate patient flow at their sites and submit recruitment histories from other trials in which they have participated. However, patient flow does not directly translate into enrollment, especially as it may relate to the specific participant requirement for the study under consideration. Investigators may estimate the recruitment based on previous trials that were not similar in scope and complexity. In addition, sites may present their successful recruitment history, but omit reference to those trials in which they were unsuccessful. Furthermore, there may be simultaneous “competing” trials at some of the sites which limit enrollment into the present study.

As a study progresses, sites tend to fall into the categories of strong and weak enrollers. As enrollment goals slip farther behind, the study’s coordinating center leaders almost always decide to allow the strong enrollers to “over-recruit” to make up for the weaker enrollers in order to meet the overall sample size goal. Since part of the selection of sites usually involves balance among the sites in terms of geography, type of clinic, racial and ethnic diversity of sample, the post-design imbalance in enrollment among the sites often accentuates site differences, impacting statistical analysis in a manner rarely considered. It is important, then, that study procedures include recruitment plans and a sufficient budget to attain the proposed recruitment and retention.

Ensuring Diversity

Studies should make robust plans for enrolling diverse research participants. Too often diversity is conceptualized too narrowly – considering, for example, only a single racial population instead of a broad concept that considers socioeconomic status (SES) and

other factors. Many of the sites selected for participation in multi-site trials are either not located in areas that have diverse populations or have not successfully engaged the diverse communities in their area. Furthermore, the staff at the sites should reflect the diverse ethnic, racial and SES groups that they would like to attract to the study. Studies often do not assemble senior research teams with enough diversity in terms of discipline, experience, language proficiency, and cultural knowledge. This lack of staff diversity should be addressed as the study is conceptualized, since diverse staff is needed to ensure that participants with diverse backgrounds can be effectively enrolled and retained in the study.

Even when populations with diverse backgrounds are attracted to trials, studies often are not prepared to accommodate them. For instance, study instruments and consent documents may be written in English only and study clinicians and staff may speak only English, which excludes non-English speaking people. Also, people with limited literacy and cognitive abilities often are not enrolled because the study does not provide alternative ways of assessing informed consent, diagnosis, or possibly even providing treatment.

These and other limitations often result in research participants who are generally homogeneous with regard to ethnicity, race, SES, language, cognitive ability and living situation. The small percentage of the sample that is considered “minority” often is combined into one “group” and often becomes a “subpopulation” considered for sub-group analysis. However, since the studies are not powered for analyses of subpopulations, little, if any, meaningful subgroup analyses are possible, and the most that can be done are “exploratory” analyses. Indeed, if subpopulation differences truly exist, they may continue to be obscured by results of these studies. Furthermore, analyzing study data by grouping all people of a particular background together may not provide useful information, and such analyses can even lead to harmful stereotypical conclusions. Investigators need to make careful decisions about the meaning of diversity in the treatments being provided so that when there is reason to expect important differences in response, the study can focus on this as a major study aim.

The more heterogeneous the population, the larger the sample size needed to detect a given difference in a homogeneous subgroup within the population. This illustrates the interconnectedness of all the issues involved in designing clinical trials. In conducting such trials, it is critical that sample size estimates include a realistic estimate of the diversity of the sample and that engagement, recruitment and retention strategies and assessment techniques are designed to appropriately support the study of participants of diverse backgrounds.

OTHER POTENTIAL PROBLEMS IN CLINCIAL TRIALS

Experience and Infrastructure

Large multi-trials can experience operational difficulties resulting from investigator inexperience with multi-site trials that require central coordination of individual sites. Most investigators conducting multi-site trials will have had experience running small

clinical trials at a single site, either as independent studies or as a site in a multi-site trial. However, skills developed for single site management do not translate necessarily to preparedness to run a multi-site coordinating center. This lack of experience is often evident even in the planning stages. The effort and resources required to be a coordinating center are almost universally underestimated, resulting in applications which are all too often under staffed and under funded. Often, applicants actually describe a data management center, rather than an operational center; instead, operational center tasks are proposed for distribution among the sites. There is little description of where the responsibilities for overall trial coordination will lie or how to implement the study over the proposed time period. Because of this, funding, staff qualifications, and allocation of staff resources for managing the study are not anticipated or detailed before the study is undertaken. Data management is important, but it is usually a separate activity from coordination activities. The proposed national electronic clinical trials data network, NECTAR, should play an important role in data management and data sharing in multi-site trials.

Once a study is underway, it may become obvious that there are inadequate monitoring systems (tracking, oversight, feedback) in place to anticipate or identify problems early. Investigators almost always recognize the need for data management systems to collect and check the data and to create databases for the statistical analyses. However, strong study management systems to provide timely feedback are delayed in development and are usually in response to urgent problems rather than in anticipation of problems. Multi-site studies need coordinating centers with strong quality assessment and fidelity assessment systems to monitor sites against protocol deviations and differences in treatment delivery.

The long-term nature of many multi-site clinical trials, with some lasting five or more years – makes it likely that there will be staff attrition at both the clinical sites and the coordinating and data management centers. A strong coordinating center should plan for training and certification of replacement staff and understand the need for extra monitoring and attention at sites during transitions. Retraining and re-certification of staff may be necessary throughout the study to keep it focused and on its original timetable.

Independence and Leadership

Problems arise when the coordinating center role is not distinct from other roles in the project, that is, when one of the participating sites also serves as the coordinating center and data management center. Conceptualizing the coordinating center independently from the data collection sites has many benefits. The scientific aspects of coordination become a focus of attention and discussion. During study implementation the coordinating investigators need to review data without allowing knowledge of accumulating data to influence decision-making at the site level. If the organizational infrastructure is such that a field site serves that dual role, there must be clear lines of responsibility, confidentiality of data, and a strong firewall to prevent any cross talk. This is extraordinarily difficult to achieve when the roles are mixed. Furthermore, there may be a conflict if the clinical site is not performing well and it is also the coordinating center.

It can be an especially difficult role for the leader of a multi-site study to lead among his or her peers. The leader must have a clear mandate from colleagues to take a leadership role, and often this is not the case. The leader must have the experience and confidence to be able to consider all points of view and then guide the Steering Committee to make a decision in spite of disagreement. Some studies suffer from too much indecision and are hampered by trying to accommodate all points of view. Studies may lose the focus of their original analytic questions as they expand to accommodate new questions. It is important for the leadership to understand that one study, regardless of size or complexity, cannot answer all questions.

Scope of Questions

The questions posed by a multi-site study should be those with broader public health significance rather than those posed in smaller, more limited single-site studies. By definition, the study population in a multi-site trial will be more heterogeneous and procedures will differ from those in a single-site efficacy trial. Coordinating centers must understand the potential sources of conflict, monitor adherence to the agreed upon protocol and be prepared to assist with difficult decisions.

Summary

These myriad problems can lead to trials that may be poorly conducted, compromised in quality, under-enrolled, and require extended time, additional funds and more personnel for completion. Prevention through good planning, careful monitoring, and effective problem solving can avert these problems. Once the NIMH has invested large sums of money in these trials, it is difficult not to add the additional money needed to “save” them, that is, fund an extension in order to finish the trial. When adding more money is not an option, the trial group is asked to re-think the hypotheses and scale back the questions in order to salvage something from the investment. Low recruitment and other operational aspects of a trial may cause investigators to lose enthusiasm or go on to new projects. Occasionally, a trial may be discontinued altogether, with no outcome, and the investment lost.

SOLUTIONS: TRUCTURING THE RELATIONSHIP BETWEEN INVESTIGATORS AND NIMH

Given the relatively early stage of experience with large multi-site trials, and their special needs, it makes sense that NIMH staff work closely with investigators at all phases of the work. Workgroup members emphasized that this should be a “collaborative” process between investigators and NIMH staff from the start –i.e., as the study is conceptualized, and this experience can be shared. In addition, structuring an ongoing collaborative relationship between investigators in the field and NIMH staff will encourage ongoing dialogue about the myriad scientific and operational issues that surround these studies.

One way to organize thinking about the process of developing and implementing a large clinical trial is to use the Consort Guidelines as organizing principles. Although these guidelines were written as publication standards, they are important because they can

serve as a roadmap to identify important components and pathways in study implementation to ensure these are a focus of investigator planning, reviewer consideration, and NIMH guidance and oversight. Investigators are encouraged to consider them during the design of a study (www.consort-statement.org).

Planning and Early Application Phase

There are few options to fix a study after it has begun. Thus, detailed planning of all aspects of study design and implementation is critical to ensure success once a trial is funded. Early in the planning, according to NIH policy <http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-02-004.html>, investigators must notify program staff about studies that will require direct costs of at least $500,000 for any given year of funding and must get approval to submit the application for peer review. This requirement provides an opportunity for the investigator. At this first point of contact, program staff could encourage investigators to enter into an ongoing collaborative relationship with program staff in planning a multi-site application, which ideally would begin with an in-person meeting. NIMH program staff has not only scientific expertise but also extensive operations and recruitment experience from oversight on a large number of trials. Program staff can use this expertise to both provide helpful consultation to ensure that investigators provide adequate information on a variety of detailed and important operational issues specific to large trials. An example of a checklist of some of these is included here in Appendix C.

Those investigators who choose not to make use of NIMH consultation would receive this checklist to review on their own. Failure to address the checklist items should be grounds for non-approval to submit the application for peer review. Those applications less than $500,000 could still submit since they are not required to have this prior approval. Although not required, similar consultation with NIMH staff would be advantageous for smaller studies as well.

Ideally, the planning process will be interactive between investigators and NIMH program staff. Investigators would be encouraged to state clear hypotheses and develop operationally feasible designs to address the hypotheses. Attention would be devoted to the relationship between design elements and methods and procedures to ensure their achievement. This is particularly relevant to the ability to recruit and retain participants, and may require that investigators include collaboration with those in other disciplines in their own communities as well as NIMH staff. Investigators need to outline realistic approaches to recruitment of participants, i.e., exactly what kinds of participants are needed, in what settings are those participants likely to be found, and what types of recruitment strategies are likely to be successful. Multiple strategies for the inclusion of historically underserved populations should be considered early in the design and planning stages and necessary preparations in terms of materials, treatment center staffing goals and specific community outreach strategies should be included in the plans.

In the proposed collaborative model, program staff and investigators would work together in the planning phase of the proposal. Sufficient time would be allotted to this activity to allow the team the opportunity to review the checklist items and feel confident that a

multi-site design is truly warranted by both the scientific and public health importance of the study questions as well as the power and sample size estimates. Program staff would advise investigators that for studies requiring large sample sizes in populations where experience indicates limited potential to enroll a sufficiently large sample size, they may be asked to present pilot and feasibility data before a larger trial could be launched. Program staff could also advise investigators to carefully review their power estimates, and alert investigators to the pitfalls of compromised or biased estimates of differences that result in sample sizes lower than what will eventually be needed to adequately test study hypotheses.

Program staff can advise investigators on a variety of operational planning issues as well. Program staff can help investigators understand the need for a separate coordinating group and the resources required. Realistic timetables, plans for piloting where appropriate, and realistic budgets for coordination, data management, and community engagement activities are all areas where program staff may provide helpful input to investigators. Program staff can also assist investigators in the development of plans, materials and community outreach strategies that can help the study achieve its recruitment and retention goals for every group considered for inclusion. Language and cultural considerations can also be discussed with program staff for suggestions of available resources. Lastly, investigators would be advised to include adequate and appropriate independent statistical and computer programming capability, preferably within the data management center.

Review Phase

During the initial scientific review, reviewers should carefully scrutinize operational capacity in addition to scientific quality and public health relevance. In order to do this, review committees must include members with extensive expertise in clinical trial design and operations, preferably those who have experience in conducting large-scale efficacy or effectiveness trials. Diversity of various kinds among the reviewers will strengthen the review for all aspects of an application.

Operational capacity should be described in a separate application or separate portion of the application, so that reviewers may evaluate the feasibility of operations plans apart from the science. Reviewers should use checklists similar to the one in Appendix C in order to systematically assess that relevant operational issues have been addressed. Reviewers should devote attention to such infrastructure components as coordinating center roles, lines of authority, autonomy of functions, and plans for monitoring study progress and treatment and assessment adherence.

Other issues that would be addressed in the review phase would include study committee structure, processes for resolving disputes and disagreements, and conditions under which a site may be terminated. The experience and expertise of the proposed study leaders should be evaluated specifically. The application should describe plans for the development of necessary monitoring tools such as enrollment tracking, assessment scheduling and tracking, tracking of completeness of data and trends in dropout. The

application must contain provisions for appropriate biostatistical and computer programming staff.

Recruitment and retention plans require specific attention in review. Reviewers should be provided sufficient information to evaluate the track records of proposed sites in terms of successes and failures as well as the potential for recruiting and retaining the specific type of participants needed. Numbers of eligible participants in the practice or catchment area should be given as well as realistic estimates of enrollment, using criteria similar to the specific inclusion criteria of the study. The application should include the number and types of competing trials at an applicant site. Thus, the reviewers should be provided information to allow them to gauge if enrollment goals are realistic for the type of study proposed. In addition, applicants should describe how study interventions would be reimbursed as this could impact recruitment and retention.

Reviewers need to incorporate specific comments related to the operational readiness of the project. One suggestion is to create an “operations bar” (similar to a “human subjects bar”) that would preclude the trial from being funded until the weak areas in operations are adequately addressed. Program staff would need guidance from review as to what would satisfy removal of the bar. Another suggestion is to use a rating scale that would indicate the operational competence score for the proposed study. This would be similar to evaluating the different “cores” in a Center application. Then program staff would have a better indication of both the strong and weak areas as assessed by the reviewers. Thus, a study with a strong scientific component but a weak operations component would not be considered fundable unless program staff thought the operational deficiencies were easily correctable without a resubmission of a revised grant application.

Council Review Phase

The Council’s review of peer-reviewed grants should consider both portfolio balance and the adequacy of the proposal for carrying out the study’s objectives when it makes funding recommendations to the Institute. The Council should recommend that an application, even if it receives an excellent score in peer review, receive a low priority for funding if it does not represent an area of high public health importance or if there is evidence that the investigator is not likely to have success in implementing and finishing the proposed study.

Post-Funding Phase

If the planning and review phases are successful in approving well-designed, and operationally well-functioning multi-site trials, the studies should have a high chance of success. However, there is still the potential for problems to arise, even in the best-designed studies.

Cooperative agreement, multi-site studies should take advantage of the partnership with the government. NIMH staff is in the unique position of having participated in and observed a large number of trials across a variety of disorders and can often provide an objective voice to the Steering Committee. The broad public health perspective that

NIMH staff brings to the group can help keep the investigators on track, as well as provide technical assistance with community engagement strategies, especially when peer pressure impedes decision-making. NIMH staff can also work with the coordinating centers to provide advice and technical assistance during the planning stages, help coordinators anticipate problem areas, and help interface between the coordinating centers and data management centers to establish a structure and tools for reporting and monitoring.

In studies that are not funded as Cooperative agreements, NIMH staff can provide similar advice and technical assistance to investigators after the study has been launched, if requested. At the very least, such input can be expected on an annual basis at the time of the annual progress report, although more frequent contact may be desirable in some cases. It is policy that adequate progress reports must be submitted for review and approval by program and grants management staff before a continuation award is made.

In summary, a cooperative partnership needs to begin when multi-site studies are first conceived because it saves time and resources. Review must focus additional attention on operational capacity. Once underway, NIMH staff should continue to help coordinators anticipate problems and maintain strong oversight.

CHAPTER V
COUNCIL WORKGROUP RECOMMENDATIONS

In the course of its review of the NIMH clinical trials portfolio, the Workgroup noted the considerable strengths but also numerous limitations in particular areas of the treatment research that the NIMH supports. To address these limitations and enhance the overall ability of the NIMH to address the major scientific and public mental health issues facing the U.S, the Workgroup has proposed a series of recommendations. Those area-specific recommendations are included in Chapter IV under the appropriate section on disorder, age group and treatment modality. But in its deliberations, the Workgroup concluded that there were overarching recommendations it could make that would strengthen the entire NIMH clinical trials portfolio. These recommendations, organized into three broad categories, follow here.

CREATING THE OPTIMAL TREATMENT RESEARCH PORTFOLIO

Treatment research in mental illness has some inherent differences from other forms of biomedical research and entails some unique challenges that must be overcome. Moreover, treatment research conducted by the pharmaceutical industry typically differs in fundamental ways from the kinds of studies that are required to inform mental health care providers, administrators and policy makers. Finally, to answer many questions in the treatment of mental illness, studies of great complexity and scale are required that often exceed the capacities of any one investigator or institution to conceive and orchestrate individually. The NIMH has already launched an effort to answer important clinical therapeutic issues through the funding of large clinical trials under the contract mechanism. However, the NIMH should adopt a more proactive strategy to further develop its treatment research programs and ensure that the most important clinical therapeutic and public mental health issues are addressed in a methodologically rigorous and ecologically informative manner. This is especially important if NIMH wants future investigator-initiated grants to address these pressing clinical issues. To do this, the Workgroup makes the following recommendations:

Recommendation 1: The NIMH should establish a process to seek input from various stakeholders that will inform the direction of future treatment research, determine what studies are most needed and integrate public health interests with scientific opportunities.

Recommendation 2: The NIMH should consider new ways to expand the development of innovative psychosocial, psychopharmacological and somatic treatments. Although existing treatments have been enormously successful and have great potential to decrease burden of mental illness, they have clear limitations and there are enormous unmet therapeutic needs. Consequently, innovative treatments must be developed based on new findings in basic neuroscience and behavioral science research. To attain these goals, the NIMH should foster research ranging from treatment development to assessment of treatment efficacy/safety and effectiveness using the optimal research designs and methodologies of treatment research. To implement such research the NIMH should employ various mechanisms, including program prioritization, requests for applications, program announcements, and contracts.

Recommendation 3: The NIMH should continue to expand efforts, informed by a previous Council report (*Bridging Science and Service*), to fund treatment research that optimizes existing treatments and facilitates their integration in the range of healthcare settings. Such research should include larger community focused trials with hybrid designs that attempt to maximize the generalizability of the findings. These efforts should be informed by clinical and services researcher expertise, as well as consumer, provider and payor stakeholders to ensure that they are relevant to the needs of the community.

BUILDING CLINICAL TRIALS CAPACITY AND EXPERTISE

Adequate resources to conduct treatment research are required to advance knowledge in therapeutics and to translate it to improved care. Consistent with the NIH Roadmap emphasis on facilitating the development of new treatments and enhancing the clinical research enterprise to evaluate therapeutic agents and modalities, the Workgroup recommends the following actions:

Recommendation 4: The NIMH should develop and maintain large networks of sites reflecting community populations and relevant healthcare systems to answer important public health questions where investigator-initiated grants or pharmaceutical trials are not likely to produce studies of sufficient size and scope to provide robust answers.

Recommendation 5: The NIMH should expand its efforts to involve historically under-represented populations in clinical research including women, ethnic and racial populations and children and the elderly.

Recommendation 6: The NIMH should issue special career development award and training announcements to increase the number of investigators capable of conducting clinical treatment research in mental illness.

Recommendation 7: The NIMH should facilitate research by standardizing data acquisition and developing central data repositories to make data from completed studies more widely available for scientists and the public.

Recommendation 8: The NIMH should support the development of core resources to facilitate the capacity of investigators, particularly young investigators or investigators lacking research experience and infrastructure, to conduct treatment research. These resources might include study coordination, community engagement training, data management, statistical planning and analyses, as well as data and safety monitoring.

Recommendation 9: The NIMH should encourage innovative research designs, high impact studies, and the development of the large trial networks and core resources to enhance the science and public health value of clinical trials research.

Recommendation 10: The NIMH should seek to partner with other agencies to facilitate the development and optimization of treatments potentially including the Food and Drug Administration (FDA) and the Substance Abuse and Mental Health Services Administration (SAMSHA), as well as the pharmaceutical industry.

Recommendation 11: The NIMH should seek to improve the translation of clinical trials research results into clinical practice.

IMPROVING THE OPERATION, EFFICIENCY AND PRODUCTIVITY OF CLINICAL TRIALS

Clinical research and the clinical trials program of NIMH are important and expanding enterprises of mental health research. Thus, it is critical to improve the scientific and operational efficiency through cooperation between NIMH staff and investigators. To ensure that the opportunities for successful studies are realized, the Workgroup recommends the following actions:

Recommendation 12: The NIMH staff with relevant expertise in clinical trials should work with all potential grantees as they develop their research applications.

Recommendation 13: Applicants should provide information outlined in the guidance developed for this report (Appendix C). If permissible at NIH, failure to provide this information should be grounds for non-approval to submit an application with costs of $500,000 or greater. If not permissible, the reviewers and NIMH staff should consider these issues in the review and award of the study.

Recommendation 14: IRG review of grant applications for treatment research should take into account the overall competence and expertise of the investigators to conduct clinical trials. Review should include specific comments related to the operational capability of the project and should be considered in the overall scoring of the application.

Recommendation 15: The NIMH staff should scrutinize the operational feasibility of a study and recommend to the NAMHC low funding priority for those proposed studies when there is evidence that successful implementation is unlikely.

Recommendation 16: The NAMHC should consider the public health importance and NIMH portfolio balance of the proposed study in considering low or high funding priority.

Recommendation 17: The NIMH should systematically consider converting large complex treatment studies into cooperative agreements. The cooperative agreement mechanism facilitates cooperation between NIMH and grantees as a means of improving efficiency and performance.

APPENDIX A

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APPENDIX C

SAMPLE CHECKLIST FOR EVALUATING THE OPERATIONS PROPOSAL FOR MULTI-SITE STUDIES

DESIGN

- The design contains estimates of power and sample size that are representative of prior results and reasonable estimates of effect size, variability, etc.
- The design includes assessment and treatment strategies that are likely to foster enrollment and retention of those who are considered for participation.
- The inclusion criteria fit the study questions, but are not so narrow that sites will have unusual difficulty finding people who qualify for the study.
- The design is flexible enough to permit enrollment of a diverse sample.
- Language and reading skills of proposed participants are taken into consideration.
- Appropriate and realistic recruitment strategies are defined and appropriately budgeted for all populations especially participants with diverse ethnic, racial, and SES backgrounds.
- All relevant aspects of the methodology including recruitment, screening, assessment, randomization procedures, treatment, data entry, etc. are appropriately piloted before beginning a large study.
- Enough developmental time has been allowed in the overall plans to allow realistically for protocol finalization, IRB approvals, development of treatment materials (e.g., manuals), piloting, training for all staff, certification, development of data collection instruments and systems, tools for quality control, acquisition of treatment products and matching placebo, etc.

SITES

- Sites are chosen for both the appropriate population and the realistic likelihood of recruitment success. In most cases this means they have provided past recruitment histories for all populations who are seen at that site.
- Recruitment histories are specific enough to the proposed research population in order to evaluate likelihood of success for this study.
- Plans are provided for “backup” sites, should they become necessary. Consideration is given to the impact of potential unbalanced enrollment across sites.
- Recruitment and retention strategies are planned with the research populations in mind. This will likely require consultation or collaboration with experts/leaders from the communities. Alternate strategies for community engagement are considered.
- Plans are established for retention of participants throughout the study.

DIVERSITY

- Sites should be considered and chosen based on various characteristics relevant for the specific aims of the proposed study. Among those should be the ethnic,

racial and/or economic diversity of the population served at that site as well as the staff who care for them.

- The research team should include direct participation of peers who are knowledgeable about the community.
- Sites should have demonstrated experience in community engagement through outreach and/or provision of services to the community and/or a very detailed and piloted plan for this outreach.
- Backgrounds of senior study staff need to reflect the diversity of the communities they wish to engage for participation in the study.
- There are plans to provide assessment instruments and other study documents (consents, information) in relevant languages. These instruments should be validated in those languages.
- Assessment instruments and all other study relevant documents (consents, information) take into account differing levels of cognitive and literacy abilities.

COORDINATING CENTER

- Independent, autonomous coordinating and data management center(s) is (are) proposed. This can be located at one of the participating sites as long as it meets criteria for independent operation and authority.
- The duties and functions of the coordinating center(s) are well specified and described in the application.
- The coordinating center(s) has expertise in multi-site leadership and/or can demonstrate adequately how they will accomplish the proposed study.
- The coordinating center leaders have a clear mandate from site investigators and have demonstrated capacity to make decisions and keep the project moving forward.
- The coordinating center senior research team has the ability to appropriately assess and advise in matters concerning racial and ethnic diversity.
- There is appropriate expertise to develop consent documents appropriate for all study populations and provide guidance to sites concerning IRB and other required regulatory approvals.
- The organizational structure, including the formation of various committees necessary to carry out the project has been outlined and the administrative structure and function clearly defined.
- Processes for resolving disputes and disagreements have been specified.
- Conditions under which a site may be terminated have been specified.
- Sites that have both the staff and expertise to adhere to the common protocol have been chosen.
- There are plans for training and certification of staff at clinical sites.
- Appropriate data monitoring tools are planned.
- There are plans for ensuring and monitoring quality assessment.
- There are plans for ensuring and monitoring fidelity to the protocol.

- The coordinating team has appropriate biostatistical leadership.
- Appropriate data management and computer programming expertise are provided.