From: Harris LS (ed.) Problems of Drug Dependence, 2001: Proceedings of the 63rd Annual Scientific Meeting, The College on Problems of Drug Dependence, Inc. NIDA Research Monograph 182. Bethesda, MD: National INstitute on Drug Abuse, 2002.

SYMPOSIUM I

THE NATIONAL DRUG ABUSE TREATMENT CLINICAL TRIALS NETWORK - CHALLENGES AND OPPORTUNITIES

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INTRODUCTION

Recent advances in basic and clinical neuroscience, neuroimaging and genetics are providing a rapidly growing body of evidence about the pathophysiology and treatment of addictive disorders, and it is now widely accepted that these are chronic relapsing conditions. New medical and behavioral treatments have been shown to have efficacy, but this work has been carried out primarily in academic treatment research environments, by highly specialized staff, and with patient populations defined by restrictive inclusion and exclusion criteria. Translating these new treatments to the broader community is an important public health challenge that was highlighted in a 1998 Institute of Medicine Report, *Bridging the Gap* between *Research and Practice,* and which is now the focus of the National Drug Abuse Clinical Trials Network launched by the National Institute on Drug Abuse in late 1999. The goal of this symposium, at the 63rd Annual Scientific Meeting of the College on Problems of Drug Dependence, was to provide meeting attendees with an overview of the Clinical Trials Network and its associated challenges and opportunities.

In an effort to address the gap between research and practice, the Institute of Medicine (IOM) formed a Committee on Community-Based Drug Treatment Research in 1998. Sponsored by CSAT and NIDA, the Committee was charged to identify relevant treatment strategies and promising research approaches, ways for community-based organizations (CBOs) to participate in and use research, technology transfer strategies, barriers inhibiting application of research, barriers inhibiting collaborative research, and strategies to overcome those barriers.

The Committee found that:

- research findings can be applied to clinical settings
- most treatment programs do not participate in research
- investigators rarely collaborate with community-based drug abuse treatment
- State and Federal policies often do not consider research findings
- consumers are rarely involved in application of research, and
- research and clinical staff need training.

Moreover, there are four factors that inhibit the diffusion of knowledge:

- the structure of treatment
- client, provider and stakeholder diversity
- stigmatization
- and insufficient information about knowledge transfer in community-based treatment.

The Committee made several recommendations. To link research and practice, the Committee recommended building infrastructure to facilitate research in CBOs and developing research initiatives that include CBOs. To link research, policy and treatment, it recommended that states should support research/practice collaboration and that financial incentives be used to promote adoption of proven treatment strategies. Recommended strategies for knowledge development included determining if consumers receive services that have empirical support and supporting services research. Dissemination and knowledge transfer recommendations included synthesizing research for providers and policy makers and promoting evidence-based treatment guidelines. The Committee recommended informing consumers about effective treatments so that they become better advocates. Training

recommendations included supporting research training in and with CBOs, training health professionals about alcohol and drug abuse and using research findings, and training staff in CBOs to apply research findings.

Consistent with NIDA's millennial goal to improve drug abuse treatment throughout the nation using science as the vehicle, and in response to these IOM recommendations, NIDA issued an RFA in January 1999, to establish the National Drug Abuse Treatment Clinical Trials Network. The mission of the Clinical Trials Network (CTN) is to conduct studies of behavioral, pharmacological. and integrated behavioral and pharmacological treatment in rigorous, multi-site clinical trials to determine effectiveness across a broad range of community-based treatment settings and diversified patient populations and to transfer the research results to physicians, providers, and their patients in order to improve the quality of drug abuse treatment throughout the country.

THE NATIONAL DRUG ABUSE TREATMENT CLINICAL TRIALS NETWORK - ORGANIZATION AND STRUCTURE

The CTN is a national network of Nodes enabling testing of promising treatment strategies in diverse treatment settings and with diverse patient populations. Each Node has a Regional Research and Training Center (RRTC) at its hub and includes several Community-based Treatment Programs (CTPs or CBOs). In the first year, NIDA funded six Nodes (New England, New York, Delaware Valley, Mid-Atlantic, Pacific and Oregon). Eight additional Nodes were funded a year later (Southeastern, Florida, Ohio Valley, Great Lakes, Rocky Mountain, Washington, Long Island, and North Carolina). The CTN is a unique network of researchers and treatment providers, combining providers' input in shaping the research agenda, a cadre of dedicated researchers, a network infrastructure to enhance study enrollment, and a large diverse provider and clinical population.

Beginning in 2000, the CTN began building and maintaining an infrastructure to support its tnission and fulfill its mandate. The structure of the CTN bears some similarities to the clinical trials networks targeted on AIDS, cancer, and other areas established by other NIH Institutes. A CTN Steering Committee, which governs the CTN, includes a principal investigator and CTP representative from each Node and two NIDA representatives. This group reviews and approves the research agenda, formulates and monitors politics and procedures guiding the research activities, and oversees communications within the CTN, as well as with the greater scientific community and the public. The Steering Committee oversees the work of a Publications Subcommittee, a Concept/Protocol Review Subcommittee, a Dissemination Subcommittee and a developing number of issue-focused workgroups. A small Operations Committee, which reports to the Steering Committee, oversees day-to-day protocol implementation and management and the activities of a Training Subcommittee, a Data Management Subcommittee, a Quality Assurance Subcommittee, and a Regulatory Affairs Subcommittee, as well as the individual Protocol and Project Teams.

A CTN Ad Hoc Oversight Board, chaired by the NIDA Director, oversees all activities conducted by the CTN. The Board advises NIDA on the programmatic advisability of proceeding with studies proposed by the Network Steering Committee and assists the Institute in prioritizing and approving research concepts. The Data and Safety Monitoring Board (DSMB) oversees and monitors the conduct of the clinical trials to ensure the safety of participants and the validity and integrity of the data. The DSMB, which includes experts from several disciplines, also makes an independent assessment of treatment effectiveness and whether or not a trial will continue. An independent NIDA Protocol Review Board reviews the final draft of all protocols submitted by the CTN Steering Committee for scientific and regulatory approval.

THE CTN RESEARCH AGENDA

Research protocol concepts are generated from CTN Nodes in collaboration with the CTPs, with the goal of creating a study that is relevant to CTP daily practice, likely to be applied after the study ends if results are positive, and pose questions that can be tested empirically. Concepts are initially reviewed by the Concept/Protocol Review Subcommittee, then by the Steering Committee and finally by the CTN Ad Hoc Oversight Board. Criteria for selection include the efficacy/scientific credibility of the proposed research, feasibility to implement in CTPs and via the CTN mechanism, public health significance and special considerations such as relevance to HIV and other infectious diseases or to women and minorities. Once approved, a Lead Investigator is appointed by the Steering Committee and a broadly representative Protocol Team is established. All protocols take advantage of the expertise

of the Regulatory, Training, QA and Data Subcommittees, as well as the PIs at all the Nodes. CTPs are represented on each of these committees and also review protocols in the early stages of development. An iterative protocol development and review process assures broad input and buy-in prior to final review and approval.

While many concepts were considered early on, including adolescents and patients in the criminal justice system, the first wave of CTN protocols, all of which were initiated in 2001, includes three buprenorphine/naloxone protocols, a motivational enhancement therapy protocol, a motivational interviewing (MI) protocol, and two motivational incentives protocols. Altogether, these protocols have been implemented in over 50 CTPs and in all 14 of the Nodes.

A second wave of protocols is expected to be initiated in late 2001 or early 2002, and includes a quantitative and qualitative assessment of CTN programs, a smoking cessation treatment protocol, a buprenorphine/naloxone adolescent protocol, a focused aftercare protocol and a protocol focusing on screening and treatment of infections (HIV, HCV, TB, STDs) amongst participants in substance abuse treatment programs.

A third wave of protocol concepts generated seventeen new proposals in areas ranging from pharmacotherapies to behavioral and family therapies, including proposals emphasizing a number of special populations (e.g., adolescents, patients with AIDS/HIV and HCV, court diverted patients, those with psychiatric and/or medical comorbidity, women and trauma).

Special interest groups that have been set up are beginning to provide a snapshot of the current state of relevant issues, to identify empirically supported interventions, to develop research concepts and appropriate special assessment tools, to develop long range research plans, and to serve as expert resources. Current special interest groups include: HIV/AIDS, Adolescent, Women and Gender, Co-morbidity, Court involved patients, and Pharmacological Treatment.

BREAKING DOWN BARRIERS - THE CHALLENGES OF TRANSLATING CLINICAL RESEARCH INTO EFFECTIVE PRACTICE

Historically, tensions and structural obstacles have inhibited research implementation in CTPs. After extensive input and comment from representatives of the research and CTP communities, it seems clear that the inception of NIDA's CTN initiative is viewed as a potential watershed in bridging the research to practice gap.

Prior to the inception of the CTN, it was common for research to be initiated by and concluded at the university with CTPs' role limited to providing sites and subjects. CTPs often had minimal input and tended to feel subordinate in the relationship. Researchers noted that CTPs were sometimes less than receptive to examination of their habitual practice and therefore shunned research, while CTPs viewed researchers as unacquainted with and disinterested in the realities of community-based practice.

There are many challenges to forging a truly integrated and collaborative process. Functional partnerships follow from mutual acknowledgment of complementary strengths while taking into account differing particular needs and missions. The relevance and sustainability of research must be balanced with the need for research validity and reliability. Additionally, individual program circumstances must be balanced against the need for common language across locations and studies. In addition to "cross-cultural" issues, CTPs also confront significant practical burdens ranging from giving over space and additional "elective" tasks to already overburdened personnel, to staff turnover. The experience of the CTN to date indicates that CTPs will fully participate in the research process when certain conditions are met. The CTP representatives need to be involved in the design from the very beginning, they need to perceive the research as meaningful, relevant and productive, and they need to be assured that the additional costs of research are supported by the grant.

Research dissemination also represents a significant challenge since clinicians have often been more interested in journals describing treatment methods and histories of individuals who have recovered, than in studying the findings of controlled studies such as are published in academic journals. In turn, researchers sometimes dismiss "clinical experience" as meaningless unless it can be supported by a controlled study. Each method can provide valuable information. Clinical observations have led to important and clinically relevant research studies. Some recent

examples are studies showing that integrating psychiatric and medical treatment with substance-focused interventions can improve compliance and outcomes for selected groups of patients, or studies showing strong associations between positive outcomes and participation in self-help groups. The CTN aims to improve treatment by helping researchers better understand the challenges of treatment providers, while also helping providers better understand research communications and methods. The CTN's emphasis on collaboration from the level of protocol development to their implementation and reporting of results will help bridge the gap that was identified in the IOM report.

For example, user-friendly publications such as NIDA Notes will be used to orient CTPs to general principles of research. Developing career track CTP in-house specialists in research could make available regular on-site training for interested staff as well as complement researchers' contributions to CTP education. Similarly, through paid fellowships, researchers could familiarize themselves with the day-to-day issues of treatment. These cross-training experiences would be mutually beneficial and enriching and would constitute another milestone in the collaborative process.

Since CTP staff also value face-to-face contact as a means of promoting understanding and trust, cross-training experiences could be further advanced with this personal ingredient in the education process. Through this trust-building exercise, researchers could also develop a fuller understanding of the norms of clinical cultures and enhanced appreciation of the need for an interactive experience that over time could promote learning and an increased appetite for research.

A key factor in CTP receptivity to research is intrinsic to the organizational culture. Thus, behavior change is more likely to occur in *"learning organizations"* that continually expand their ability to shape their future than organizational cultures that are *entrenched in the status quo* and committed to existing views. However, each new growth experience will increase the potential for openness to change.

The necessary ingredients for the evolution of an enhanced partnership are embodied in the structure of the CTN. Considerable headway has already been realized towards the goal of inclusion through activities ranging from joint selection of research concepts and joint review at all stages of the protocol development process, through to meaningful and efficiently designed studies supported by additional manpower and fiscal resources. CTP/researcher partnerships have been and will continue to be a springboard to effectively integrate new skills into the permanent treatment armamentarium.

POLICY AND FISCAL HURDLES TO IMPLEMENTATION OF CLINICAL TRIALS IN THE COMMUNITY

There are several challenging funding issues facing CTN-affiliated CTPs. CTPs have joined the CTN because of their commitment to advance treatment knowledge and not because of financial benefit. However, CTPs can not be expected to lose money in the conduct of CTN protocols. Thus, contracts between the RRTCs and the CTPs must ensure that basic fairness exists in regard to how research costs and particularly routine care costs are addressed. NIDA and the RRTCs must work to educate third party payers about the profound value of supporting these trials.

A serious risk facing the CTPs is the possibility that in some cases they may not receive full reimbursement for the routine costs of care from third party payers because the protocol may be considered to be investigational or experimental. Not at issue are the research costs of care. Those costs are built into the Cooperative Agreements between NIDA and the RRTCs. It is, however, less clear how much, if any, of the routine care costs are budgeted into the Cooperative Agreements. If third party payers do not reimburse the CTPs for the routine costs of care, it is likely that such costs will have to be paid from the Cooperative Agreements. This will reduce the amount of funding available for the conduct of research and will complicate the relationship between the RRTC and the CTP as they negotiate mechanisms for payment of these costs. In this regard, care must be taken within the Node and across Nodes to ensure that CTPs are treated with consistency in terms of what treatment costs will be allowable to charge against the subcontract between the RRTC and the CTP.

Under NIH policy, the RRTCs and, in turn, the CTPs, are obligated to seek reimbursement for usual patient care costs which is defined as "care that would have been incurred even if the research study did not exist." The policy

states that usual care (routine care) costs will not be supported unless the PI grants an exception based upon a finding that meets the terms of the NIH Grant Policy.[1] It will be important to pay close attention to this during CTN start-up to assure that CTPs across Nodes are treated similarly. The Steering Committee may later need to develop criteria for granting relevant exceptions.

The issue of third party reimbursement of routine care costs emanating from clinical trials has received a good deal of attention over the past several years, largely driven by the changes in financing health care brought about by managed care. The result is that it is now less predictable whether or not a payer will reimburse for routine care under a clinical trial, thus making it more difficult to recruit patients into clinical trials. The moving force behind much of the recent attention to this issue comes from the cancer treatment community. The National Cancer Institute (NCI) has successfully negotiated agreements with DOD, VA and some health plans covering the routine care costs of treatment. NCI's Community Oncology Program, which has some features similar to the NIDA CTN, strictly prohibits the use of grant funds for the clinical care of patients.[2]

NIH has been concerned that the lack of a clear policy by third party payers on the reimbursement of routine clinical care, particularly insurers and Medicare, has had a chilling effect on the recruitment of patients into clinical trials. The NIH has entered into an agreement with the American Association of Health Plans (AAHP) in which the AAHP will encourage its members to reimburse for routine care costs, provided that reimbursement is not substantially higher than what a health plan would incur in providing standard treatment by an in-network provider.[3] As a possible precursor to the problems that CTPs might experience, NIH and the AAHP have not been able to implement the agreement because, among others things, they can not agree on what constitutes routine care costs.

The General Accounting Office has also studied this issue and concluded, to the dismay of NIH, that there is little evidence that recruitment into clinical trials has been adversely affected by the lack of a clearly stated policy on clinical trial reimbursement by insurers.'

A more successful outcome has arisen from an IOM study of Medicare policy on clinical trial reimbursement. Here, Medicare limits reimbursement to care that is reasonable and necessary but had not articulated a policy on the reimbursement of care under clinical trials. The IOM found that the Medicare fiscal intermediaries were reimbursing for such costs because, in many cases, they were not aware that treatment was being performed under a clinical trial.[5] Based upon the IOM report, then President Clinton issued an Executive Memorandum authorizing Medicare to pay for routine care costs as well as the costs due to medical complications from such trials. This action may portend similar action by the insurance industry as may be prompted by Congressional interest in the issue.

Since a significant portion of many of the CTP's budgets come from Federal, State and local funding, it is likely that there will be little or no restriction on how they will use those funds to cover the costs of care. The big question will be whether or not the State Medicaid programs will reimburse for such costs, if the State is made aware that the costs were incurred in a clinical trial. The consensus from HCFA Medicaid staff is that Medicaid could represent a problem to the CTPs.

Faced with what could be a substantial funding issue for the CTN, NIDA has embarked on an educational effort to inform managed care organizations and managed behavioral health care organizations about the CTN and the importance of supporting routine care costs. NIDA has entered into an alliance with the American Managed Behavioral Healthcare Association in this educational effort.

The NIH, IOM and GAO reports suggest that the CTPs can take some advance preparatory action with third party payers to help make their case for reimbursement. The CTPs should be prepared to demonstrate the following: that the trial is based upon scientific evidence of efficacy; that the trial is based on a randomized, controlled design, answering "real world questions" of potential importance to payers; the multi-geographical nature of the study; the rigor of protocol selection; the support of other credible organizations like NIH, NIDA and the RRTC; that the treatment was medically necessary and the protocol derived from a rigorous IRB process with informed consent; and the legitimacy of costs claimed as routine care. It will also be helpful as protocols are developed and approved, to clearly identify the categories of routine costs and research costs associated with each protocol.

NIDA and the Steering Committee are well on the way to addressing the issue of funding for routine care costs and through their educational efforts could make an important contribution to funding parity for drug treatment.

CHALLENGES AND OPPORTUNITIES

There are more than enough challenges for the CTN as it attempts to blend research and practice, primarily revolving around expertise, the research agenda and research implementation. With both researchers and practitioners bringing their experience to bear, building mutual trust and respect is critical to the success of the partnership. A balance needs to be found between researchers' need for scientific rigor and practitioners' requirements of relevance and cost (i.e. the likelihood that study findings would be able to be applied). The partnership and the national scope of the CTN creates design challenges as well, in areas such as baseline treatment variations, inclusion/exclusion criteria and the choice of interventions that can be used. Challenges for implementation include making protocols user friendly, taking a bottom line approach, using common language, effective training, using common assessment batteries, and open vs. blinded results to therapists.

These challenges are viewed as opportunities as the CTN has great potential for applied treatment research, including research on treatment delivery, genetics, special populations, medications usage development, behavior therapy transferability, large sample clinical studies, long-term treatment effect studies and more. In addition to treatment research, the CTN platform provides a way to assess cost effective process/strategy payments; practice/organizational adaptation to facilitate transfer of science-based interventions; policies to encourage adaptation; incentives to sustain new practice; and effective training strategies.

The Clinical Trials Network is an ambitious undertaking, requiring a long-term commitment from investigators, CTPs and NIDA. As complex as the partnership is, protocols have been written and put into the field in less than two years. The process has been difficult, but all signs to date are positive that the goals of the CTN can be achieved.

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