Substance Abuse and Rehabilitation

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REVIEW

The National Drug Abuse Treatment Clinical Trials Network: forging a partnership between research knowledge and community practice

This article was published in the following Dove Press journal:
Substance Abuse and Rehabilitation
30 March 2011
Number of times this article has been viewed

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Abstract: The National Drug Abuse Treatment Clinical Trials Network (CTN) has faced many challenges over its first eleven years. This review explores some of these challenges and the paths the CTN took to meet these challenges, including: designing clinical trials that reflect the CTN's mission and changing public health needs, finding the synergies in the varied expertise of clinical treatment providers and academic researchers, promoting evidence-based practices and expanding the Network into mainstream medical practices to reach a broader patient population. Included in this exploration are specific examples from CTN clinical trials.

Keywords: Clinical Trials Network, drug abuse, addiction

Introduction

The Institute of Medicine released the report, 'Bridging the Gap Between Practice and Research: Forging Partnerships with Community-Based Drug and Alcohol Treatment', in 1998, documenting the inadequate connection between research knowledge and community practice in the field of substance abuse treatment and research.[1] The report urged the responsible federal agencies to establish an infrastructure to facilitate research within community-based substance abuse treatment programs and to foster true research partnerships with treatment providers. The National Institute on Drug Abuse (NIDA) of the United States (US) National Institutes of Health subsequently established the National Drug Abuse Treatment Clinical Trials Network (CTN), with the stated goal of accelerating the translation of science-based addiction treatments into community-based practice.[2]

The CTN is organized into 13 nodes centered in university-based research centers that are aligned with healthcare providers from more than 240 community-based substance abuse treatment programs in 39 states across the nation, the District of Columbia, and Puerto Rico (Figure 1). The dozens of scientists in the network are affiliated with more than 50 universities. The network strives to foster collaboration between researchers and treatment providers throughout the entire research process, thereby enhancing the transferability and acceptability of research results by the practice community and their patients.[2] As of December 2010, researchers in the CTN have enrolled over 12,000 trial participants, completed 24 major clinical trials (Table 1), published over 190 scientific papers in peer-reviewed journals,[3] and contributed to the development of three comprehensive training and treatment tools, including Buprenorphine Treatment, Short-Term Opioid Withdrawal Using Buprenorphine, and Promoting Awareness of Motivational Incentives, for dissemination throughout the addiction treatment and research community.[4,5]

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However, implementing randomized clinical trials across multiple and diverse substance abuse treatment programs presents several unique challenges that need to be addressed in order to achieve the stated goals. In this review, we discuss the nature of these challenges and the network's strategies to address them in the following four areas:

- Designing clinical trial protocols: new trial paradigms were developed with the aim of efficiently answering the practical clinical questions that often fall outside the scope of more traditional randomized trial models.
- Implementing quality clinical trials in practice settings unfamiliar with research logistics: balance must be kept between the practical needs and research knowledge of the clinician's practice and the need to fulfill ethical, data integrity, and regulatory requirements for human subjects' protection in clinical research.
- Promoting the adoption of evidence-based treatment practices: research products must meet the community's needs and stay within community resource constraints.
- Expanding the network to include research sites that are part of US mainstream medical care: new populations of patients who do not typically seek treatment in specialty-care clinics devoted to substance abuse treatment must be reached.

Designing clinical trial protocols

The CTN's first group of studies evaluated the effectiveness of contingency management, motivational interviewing, and buprenorphine detoxification.[4] Those studies met one of the CTN's original criteria for developing new research: that the efficacy of the particular therapy under consideration for CTN testing must have been demonstrated in prior research. This criterion set the expectation that therapies selected for CTN trials would be ready to implement in "real world" settings soon after the evidence supporting their use was validated in an effectiveness trial.[6]

Because there were a limited number of interventions that had reached this late stage of development, it became necessary to apply the original criteria more judiciously for choosing promising treatment interventions. It was recognized that the network's "blended" infrastructure of researchers and community-based treatment providers lends itself to studies aimed at developing and testing interventions on which relatively little prior efficacy research has been

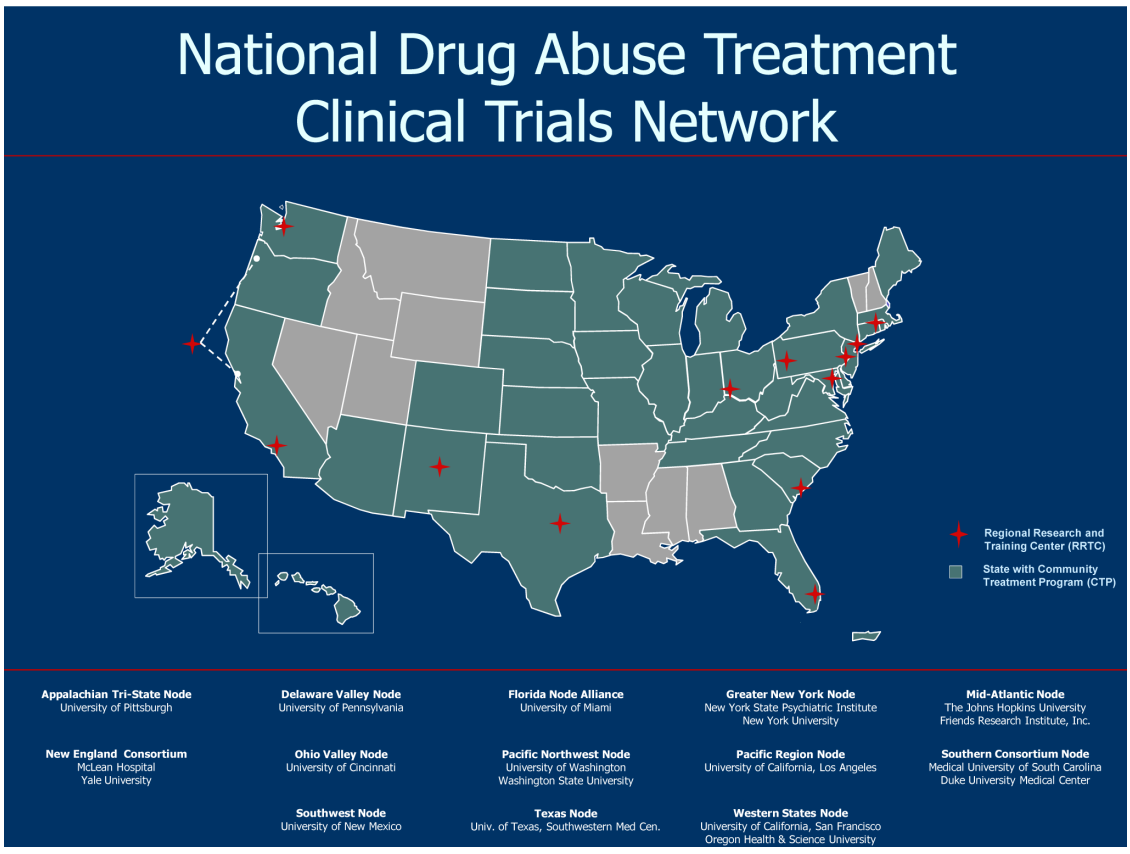

Figure 1 National Drug Abuse Treatment Clinical Trials Network.

Table 1 Status of Clinical Trials Network clinical trials (December 2010)

Protocol # (Reference[a])	Principal Investigator	Study	Sites	N	Status
CTN 0001	Ling	Buprenorphine/naloxone for inpatient detoxification	6	113	Completed (Ling 2005)[37]
CTN 0002	Ling	Buprenorphine/naloxone for outpatient detoxification	6	230	Completed (Ling 2005)[37]
CTN 0003	Ling	Comparison of two buprenorphine/naloxone taper schedules	11	516	Completed (Ling 2009)[38]
CTN 0004	Carroll	Motivational enhancement therapy for patients in treatment for substance use disorders	6	496	Completed (Ball 2007)[39]
CTN 0005	Carroll	Motivational interviewing for patients in treatment for substance use disorders	5	423	Completed (Carroll 2006)[40]
CTN 0006	Stitzer	Low cost motivational incentives for stimulant-abusing patients in outpatient psychosocial treatment programs	8	454	Completed (Petry 2005)[28]
CTN 0007	Stitzer	Low cost motivational incentives for stimulant-abusing patients in methadone maintenance treatment	6	403	Completed (Peirce 2006)[27]
CTN 0009	Reid	Incorporating smoking cessation treatment into substance abuse treatment programs	12	225	Completed (Reid 2008)[41]
CTN 0010	Woody	Buprenorphine/naloxone-facilitated rehabilitation for opioid-dependent adolescents and young adults	6	154	Completed (Woody 2008)[42]
CTN 0011	Hubbard	Telephone enhancement procedure for long-term engagement in continuing care	4	339	Completed (Hubbard 2007)[43]
CTN 0013	Winhusen	Motivational enhancement therapy for pregnant women in treatment for substance use disorders	4	200	Completed (Winhusen 2008)[44]
CTN 0014	Szapocznik, Robbins	Brief Strategic Family Therapy for adolescents in treatment for substance use disorders	8	457	Manuscript in preparation
CTN 0015	Hien	Seeking Safety therapy for women with PTSD in treatment for substance use disorders	7	353	Completed (Hien 2009)[45]
CTN 0017	Booth	HIV/HCV risk reduction interventions for injection substance users	8	632	Completed (Booth 2010)[46]
CTN 0018	Calsyn	HIV/STD risk reduction interventions for men in treatment for substance use disorders	14	594	Completed (Calsyn 2009)[47]
CTN 0019	Tross	HIV/STD risk reduction interventions for women in treatment for substance use disorders	12	517	Completed (Tross 2008)[48]
CTN 0020	Svikis	Job seekers training for patients in treatment for substance use disorders	12	628	Manuscript in preparation
CTN 0021	Carroll, Szapocznik	Motivational enhancement therapy for Spanish-speaking patients in treatment for substance use disorders	6	463	Completed (Carroll 2009)[49]
CTN 0027	Ling	Liver function in patients maintained on buprenorphine/naloxone or methadone	9	1269	Manuscript in preparation
CTN 0028	Riggs, Winhusen	Osmotic-release methylphenidate for ADHD in adolescents in treatment for substance use disorders	11	303	Manuscript in preparation
CTN 0029	Somoza, Winhusen	Osmotic-release methylphenidate for ADHD in patients receiving smoking cessation treatment	6	255	Completed (Winhusen 2010)[50]
CTN 0030	Ling, Weiss	Treatment of prescription opioid addiction	11	653	Manuscript in preparation
CTN 0031	Donovan	Twelve-step engagement for patients in treatment for stimulant use disorders	10	471	Manuscript in preparation
CTN 0032	Metsch	HIV rapid testing and counseling in substance abuse treatment programs	12	1281	Manuscript in preparation
CTN 0037	Trivedi	Exercise as an adjunctive treatment for substance use disorders	9	330[b]	Enrolling
CTN 0044	Nunes	Web-delivered treatment for substance use disorders	10	500[b]	Enrolling
CTN 0046	Winhusen	Smoking cessation intervention for patients in treatment for stimulant use disorders	12	528[b]	Enrolling
CTN 0047	Bogenschutz, Donovan	Screening, motivational assessment, referral, and treatment in emergency departments	6	1285[b]	Enrolling
CTN 0048	Ling	Buprenorphine and naltrexone for treatment of cocaine dependence	12[b]	300[b]	Development
CTN 0049	Metsch	Linkage-to-care interventions for HIV-infected substance-using hospital inpatients	10[b]	800[b]	Development

Notes: [a]See References for full citation; [b]Planned study parameters.

Abbreviations: HIV, human immunodeficiency virus; HCV, hepatitis C virus; STD, sexually transmitted disease; PTSD, posttraumatic stress disorder; ADHD, attention deficit hyperactivity disorder.

conducted, with an eye on ensuring that the treatments are sustainable in actual practice. Thus, the CTN broadened its research agenda to include evaluations of an expanded range of promising treatment interventions.

In some cases, the CTN's treatment providers bring to the table experience with, or interest in, an intervention or clinical practice that is widely employed despite uncertain scientific grounding and hence warrants rigorous evaluation. One such example is Seeking Safety, an integrated cognitive-behavioral treatment intervention designed for patients with comorbid posttraumatic stress disorder (PTSD) symptoms and substance use disorders.[7] The CTN undertook a randomized multisite trial of Seeking Safety, for which there was limited empirical support at the time, because it was among the most promising approaches for targeting this type of comorbidity and had been adopted by many treatment programs.[8–11] The CTN-affiliated treatment providers' experience with this intervention contributed greatly to the success of this trial's design and execution. Two significant adaptations were made to the Seeking Safety treatment program to improve the feasibility of studying it in the CTN: 1) the number of sessions was reduced from 25 to 12; and 2) new enrollees immediately entered rolling therapy groups instead of waiting for a new group to start the program with its introductory first session. Thus, therapy groups did not consist of the same cohort of individuals from start to finish. Both adaptations were made to adjust to standard practices carried out in community treatment programs (CTPs) participating in the CTN. The study's findings have provided important support for addressing PTSD early in substance abuse treatment and have spurred further research in this area.[12]

At other times, new disorders, or newly affected populations, may rapidly emerge as urgent public health concerns. The CTN's standing translational research platform can facilitate a telescoped trial program to quickly test and refine treatment approaches that address such needs. One example is the recent increase in the prevalence of prescription opioid abuse problems in the US.[13,14] Most treatment studies of opioid-dependent populations have focused on heroin users,[15] and the utility of applying those studies' findings to a potentially quite different patient population is uncertain. Many of the CTN-affiliated treatment providers have dealt with this gap in knowledge firsthand as they see a growing number of patients with problems related to prescription opioid abuse and dependence. As a result, the CTN launched the Prescription Opioid Addiction Treatment Study in 2006 to address this pressing public health concern. Building from existing opioid dependence treatment modalities, this trial applied an innovative two-phase adaptive, sequential treatment design to test the effectiveness of buprenorphine/naloxone treatment plus individual drug counseling for opioid analgesic dependence.[16] This trial's primary outcome findings are expected to be published in 2011.

Implementing quality multisite trials in community-based treatment settings

Moving research from academic, well controlled environments to the context of community-based real world healthcare settings may strengthen the external validity of the interventions and enhance the generalizability and adoptability of study results. During the CTN's first decade, addiction treatment centers affiliated with the CTN were typically specialty substance abuse treatment programs in community settings. These have included hospital-based programs, inpatient and outpatient rehabilitation facilities, and mental health centers. CTN trials conducted in these programs have drawn upon a diverse population of treatment-seeking patients. However, the various CTPs are operated under very different treatment philosophies, funding streams, regulatory rules/policies, and organizational management and staffing.[17] These differences, in turn, impact the choice of patient populations and considerations of specific types of CTPs to be included in each CTN trial. They also influence choices of realistic primary outcome measures appropriate to the trial design.[18] For instance, the study protocol of the Motivational Incentives (also known as contingency management) trials (CTN 0006, 0007) was divided into two separate trials to address patients enrolled in two different treatment settings: methadone treatment programs and psychosocial outpatient treatment centers.

Another challenge of designing multisite, controlled effectiveness studies in the CTN involves the choice of the most appropriate comparison treatment. Experimental treatments are often added to existing or commonly used treatments in the experimental group, and the existing treatment alone is offered to participants in the control group. Many CTN trials have used Treatment as Usual (TAU) as their control condition, but the variety of treatment settings described above requires an equally wide variety of TAU practices. The actual treatment delivered at one CTP as TAU may be very different from the TAU practices delivered at another CTP.[19] To ensure the interpretability of trial findings, the CTN generally seeks to select sites with similar TAU practices for a given trial. McCarty et al baseline study results[17] and Roman et al

independent surveys[20,21] of CTPs within the CTN provide some of the information required to evaluate potential sites on this criterion. From there, study investigators survey and interview prospective CTP sites to gather more specific information about their treatment settings and TAU practices. The ultimate aims are to conduct trials with reasonably homogeneous background or control treatments, and to be able to precisely characterize these elements of the trial design.

Promoting the adoption of evidence-based treatment practices

Facilitating the dissemination of evidence-based treatments into community practice has always been an integral part of the CTN mission. The CTN established a Dissemination Subcommittee (later renamed the Research Utilization Committee) to plan and implement dissemination strategies for the network. The CTN's current dissemination strategy emphasizes a) dissemination within the CTN and b) close collaboration with the Substance Abuse and Mental Health Services Administration and other stakeholders (eg, the National Association of State Alcohol/Drug Abuse Directors) that devote considerable resources and expertise to dissemination-related research and active dissemination efforts.

Operationally, the CTN is guided by the following approaches: a) bringing researchers and providers together to generate research questions that can impact practice, b) conducting trials in real world treatment settings with diverse treatment-seeking populations to improve external validity, and c) exposing clinicians to evidence-based treatments via participation in CTN trials.[21] It is recognized that the process of disseminating research results to impact practice is slow and difficult and that it should be considered from the beginning of trial planning.[22,23]

These approaches have made a notable impact on the dissemination of motivational incentives as studied in the CTN.[4,24] CTN providers raised several major dissemination issues during the research development process. The providers objected to the high costs of, and the appropriateness of, positive reinforcement for addiction treatment; some believed that it could be counterproductive to provide incentives. Their concern regarding the cost of the incentives stemmed in part from the fixed level of reimbursement provided by third-party payers for the care of substance use disorders. Incentive payments were unlikely to be added to the reimbursement if clinically implemented, and were too costly to be supported by the provider alone.[25,26] The CTN therefore modified the research protocols to employ low-cost prize-drawing incentives that would be affordable in community programs.[24,27,28] Once these CTN studies had demonstrated the feasibility of implementing incentive procedures and showed a significant positive impact on patients' engagement in treatment and drug use, several CTN-affiliated treatment providers became early adopters and promoted the use of the intervention in their communities.[4,24,29,30]

Another dissemination example is the adoption of buprenorphine for the treatment of opioid withdrawal. The two CTN trials conducted by Ling et al[31] have demonstrated that buprenorphine/naloxone is more effective than an alternative clonidine treatment in curbing opioid withdrawal. Compared to clonidine, buprenorphine was found to be five times more effective in outpatient settings and three times more effective in inpatient settings in a 13-day detoxification schedule.[4,31] Of note, CTPs that participated in these two studies embraced these findings and almost immediately adopted buprenorphine/naloxone for short-term detoxification in their practices. This experience corroborates the concept that programs directly exposed to the research intervention are more likely to adopt it, relative to those that are not exposed.[21]

These examples clearly demonstrate that dissemination can be achieved by a) promoting the use of sound interventions that are compatible with the adopter's values and experience, b) increasing the exposure of providers/clinicians to the research process in order to engage potential early adopters, and c) encouraging early adopters to champion the use of new interventions.[22,32] Additional information from the network also has shown that the rate of uptake of research findings into practice relates only minimally to the demonstrated treatment effect size of a given intervention, but is more significantly influenced by cost and other environmental factors, such as state policies regulating treatment and general attitudes toward agonist treatment in addiction.[33]

Taken together, the CTN has continued to address the dissemination of its research products across varying settings and contexts: eg, why do established interventions lose effectiveness over days, weeks, or months? Why do tested interventions sometimes exhibit unintended effects when transferred to a new setting? How can multiple interventions be effectively packaged to capture cost efficiencies? Ultimately, it is not enough to generate evidence-based interventions; it is just as important to understand how to optimize intervention delivery in practice.[34]

Expansion of the network to address unmet needs

The CTPs participating in the CTN can reach only a small fraction of the people who need substance abuse treatment.

Recent data have indicated that of an estimated 23.5 million Americans who needed treatment for an illicit drug or alcohol use problem in 2009, only 2.6 million had actually received treatment at a specialty facility (hospital, rehabilitation facility, or mental health center) in the past year. Four million persons were treated for substance use or medical problems associated with substance use in emergency departments, private doctors' offices, prison or jail, or self-help groups.[35]

NIDA and the CTN believe that broadening the scope of the network's constituent treatment providers will broaden the scope of its research and benefit patients with substance use disorders. One significant step towards this goal is the clinical trial titled Screening Motivational Assessment and Referral to Treatment in Emergency Departments (SMART-ED). The trial is presently enrolling participants in six hospital emergency departments around the country and will evaluate a screening and brief intervention process to identify individuals with substance use, abuse, or dependence and to provide timely interventions and referral to treatment as indicated.[2]

The SMART-ED project is built on CTN-affiliated researchers' collaborations with researchers and clinicians in emergency departments. NIDA has sought to extend and formalize such outreach efforts. NIDA's 2009 funding announcement for applications to participate in the CTN requested that prospective nodes engage health service entities outside the traditional substance abuse treatment practice system.[36] In the future, this expanded network will facilitate research efforts that span the broad spectrum of treatment settings in which substance abuse patients encounter the healthcare system.

Summary and conclusion

The CTN has faced many challenges since its inception in 1999, beginning with a difficult-to-treat patient population and, initially, a lack of research experience among many of the clinicians participating in the network. Likewise, academic researchers lacked insight into the unique needs of various treatment clinics. These differing areas of expertise and perspectives initially hindered appropriate decision-making regarding what to study in the network.

The academic researchers and the community-based clinicians worked collaboratively to develop innovative research paradigms to address the practical clinical questions posed by clinicians in the CTPs and across the field at large. Rather than forcing experimental designs into standard templates, investigators in the CTN have gone outside the scope of more traditional randomized trial models to adapt research interventions to the needs of community treatment centers. Furthermore, many providers in the network had identified a clinical need and adopted the Seeking Safety intervention to treat drug-abusing patients suffering from PTSD without prior conclusive evidence of its effectiveness. Here, the CTN's role was to objectively evaluate the effectiveness of treatment interventions after their dissemination. The CTN continues to test new practices for addiction treatment for which efficacy has not been adequately characterized.

The CTN studies have shown that quality clinical trials can be successfully implemented in practice settings unfamiliar with research logistics by taking clinicians' practical needs and research knowledge level into account. The CTN has promoted the adoption of evidence-based treatment practices by researching questions posed by the treatment community and delivering treatments that do not strain community resources.

The CTN is now expanding the network to include research sites that are part of US mainstream medical care. This will allow the treatment community to reach new populations of people with substance use disorders who have not typically sought treatment in specialty care clinics devoted to substance abuse treatment. The ongoing SMART-ED study explores the value of reaching out to untreated individuals with addiction problems by engaging them in hospital emergency departments. At this time, there is little evidence of efficacy to support this strategy in substance use other than alcohol, and therefore, this study is an attempt by the CTN to expand opportunities to offer existing treatments to the segment of the drug-abusing population that utilizes the mainstream healthcare system. The challenges yet to be faced in this effort seem large, but not as large as the potential for improvements in public health.

We have sought to characterize our experiences in a few aspects of this unique venture that might generalize to other efforts of clinical research, translation, and dissemination. Fundamental to the successes of the network has been a willingness to adapt to the street-level realities of clinical research in this field while keeping an eye on the goals of the program, the expertise of the people in the network, and expert advice offered by many outside the network. We eagerly look forward to the many challenges to be faced in the future of NIDA's CTN.

Disclosure

The authors are employees of the Center for the Clinical Trials Network of the National Institute on Drug Abuse, National Institutes of Health, the funding agency for the National Drug Abuse Treatment Clinical Trials Network. The

opinions in this manuscript are those of the authors and do not represent the official position of the US government.

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