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The Design and Analysis of Multisite Effectiveness Trials: A Decade of Progress in the National Drug Abuse Clinical Trials Network

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This Special Issue brings together articles that reflect 12 years of experience in the National Institute on Drug Abuse (NIDA) Clinical Trials Network (CTN) with methodological and statistical issues that arise in the design and conduct of controlled, multisite, community-based effectiveness trials. To date, the CTN has randomized over 13,000 patients into 27 completed trials, with more trials currently ongoing, providing a wealth of experience in design, implementation, and analysis of effectiveness trials. We hope that these articles will prove useful in the future to investigators conducting effectiveness research in the addictions, as well as other branches of mental and behavioral health.

Effectiveness trials are an important step in the translational spectrum of treatment development. Efficacy trials, referred to as Stages 1 and 2 in behavioral therapy development (1), or Phase 2 or 3 in medications development, seek to establish the effect of a new treatment under ideal conditions. Typically conducted in research clinics at tertiary care centers, efficacy trials are randomized, controlled trials that place emphasis on internal validity, with attention to selection of patients, blinded, matched control conditions, and control of the background or clinical platform. Effectiveness trials address a different question, namely ‘What benefit does the new treatment convey to patients when implemented within real treatment systems in the community?’ This gets closer to estimating the potential public health impact of a new treatment. Thus, the emphasis in the design of effectiveness trials is on external validity – study samples representative of patients who actually present for treatment in the community (fewer exclusion criteria); community-based clinicians (as opposed to expert research clinicians); and community-based treatment settings with their inherent variability (2).

The NIDA established the NIDA CTN in 1999–2000 to conduct effectiveness trials of new treatments for substance abuse. A serious gap in treatment development had been highlighted by the Institute of Medicine (3), namely that treatments, both behavioral and pharmacological, developed with National Institutes of Health (NIH) funding in research programs were not reaching the treatment system, and therefore not having the chance to impact the public health (3). Effectiveness research was needed, and there had been little in the field to that point. Given that fact, it is not surprising that most of us who joined the CTN came from a tradition of efficacy research. What we have learned is that effectiveness trials

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present methodological challenges that are distinct from those of traditional efficacy trials, related to issues such as greater sample heterogeneity, and the need to address questions not just about whether a treatment works, but how the treatment works in the context of community-based treatment programs where the treatment is being applied (2,4).

The issue leads off with an article from Kathleen Carroll, providing an overview of lessons learned on the design and conduct of effectiveness trials during the first 10 years of the CTN (5). Dr. Carroll led or helped lead a number of the first group of trials of behavioral treatments conducted in CTN and was a pioneer in recognizing and handling the methodological challenges of effectiveness trials, particularly with respect to standard treatment in community treatment and what it means to test a new treatment in that context.

Next comes a series of papers about effectiveness research with particular special populations within the larger universe of substance-dependent patients. Susan Tross et al. (6) provide an overview of lessons learned on HIV risk reduction research in CTN, highlighting the effectiveness demonstrated for some of the interventions tested at lowering HIV risk behavior, but the need for research to develop more robust interventions. Don Calsyn et al. (7) provide an analysis of self-reported monogamy, showing that monogamy is complex, requiring nuance in its measurement and not necessarily associated with lower HIV risk behavior.

Shelly Greenfield et al. (8) summarize what has been learned from CTN trials about gender and the design of effectiveness trials to better elucidate the role of gender as a moderator of treatment effects. Over 40% of patients randomized into CTN trials to date have been women, who tend to differ from men in having more history of trauma, more psychiatric comorbidity, and unique issues with respect to HIV risk, among other areas. In the next article, Sudi Back et al. (9) examine differences between opioid-dependent men and women entering a trial of buprenorphine taper, highlighting how gender contributes to patient heterogeneity.

Ethnicity is another important source of heterogeneity in substance-dependent populations. Kathy Burlew et al. (10) provide an overview of lessons learned from analyses of CTN data sets examining ethnic differences in populations and outcomes, focusing on recruitment and retention, the potential impact of ethnicity on measurement of substance use and other outcomes, and data analytic issues, compiling recommendations for future research. Lisa Ray Thomas et al. (11) describe a CTN initiative to develop treatment research among Native American tribes, a group that is heavily affected by addiction, but under-represented in treatment development efforts.

The next five articles address problems in the measurement of outcome in trials of treatments for substance use and related outcomes such as trauma or HIV risk. Trivedi et al. (12) describe various possible methods of measuring stimulant use outcome considered during the design of a trial of an exercise intervention. Oden et al. (13) and Korte et al. (14) address an ongoing source of controversy for the field analytically by reporting statistical analyses comparing different methods of measuring drug use outcome by self-report, urine drug screen, and their combination. Hu et al. (15) and Bandyopadhyay et al. (16) demonstrate the problem of analyzing an outcome measure that has a skewed distribution with an excess of 0 values, so-called zero-inflated distributions. With outcomes such as substance use or HIV risk behavior patients often become “abstinent” and thus score 0, while other patients score a wide range of non-zero values. Frequent zeros may also relate to the heterogeneity and wide range of severity within the samples of effectiveness trials. Zero-inflated distributions violate the assumption of normality underlying traditional regression models, which may then yield biased estimates of the effect of a treatment in a clinical trial.

The articles explain and demonstrate the use of zero-inflated Poisson, zero-inflated negative binomial, and hurdle models, which are more appropriate for the analysis of such data.

The next three articles address the impact of the heterogeneity of clinical sites in effectiveness trials. In efficacy trials, there is usually an effort to control the background or platform treatment (e.g., the research clinic) to minimize variability. In effectiveness trials, the variation across clinical sites is instead an important variable in the analysis, reflecting real-world variations in treatment settings, the impact of which on treatment effectiveness needs to be understood. Feaster et al. (17) provide a rigorous explanation of handling of sites and site variability in the statistical models for estimating treatment effects. Lirio Covey et al. (18) provide an example with an analysis of main effect of site and site-by-treatment interaction in a six-site trial of OROS-methylphenidate for cessation intervention. Jennifer Potter et al. (19) describe considerations and methods for the selection of sites for effectiveness trials.

The next five articles describe various examples and issues in the design of effectiveness trials in the CTN. “Bidirectionality” has been an important concept in the CTN, meaning that both researchers and community-based practitioners need to participate on an equal footing in the design, analysis, and interpretation of effectiveness trials to ensure external validity. Donovan et al. (20) describe this bidirectional process in the design of a trial of a behavioral intervention for stimulant dependence. Bogenschutz et al. (21) describe the design of a trial of a screening and brief intervention for drug dependence in emergency departments. Wakim et al. (22) highlight the problem of dropout from effectiveness trials, which erodes power and raises the specter of bias due to differential attrition. They test the hypothesis that study burden will influence retention through an analysis of retention across 24 CTN studies, finding a weaker relationship than expected. Fussell et al. (23) describe the problem of training sites and their staff in research protocols and standardized patient walk-through as a training tool. Lindblad et al. (24) discuss the problem of safety reporting in clinical trials through a review of safety reporting methods in completed CTN trials. Safety reporting is a requirement that often imposes substantial assessment burden on research teams with seemingly limited yield of useful data. They propose a method for streamlining safety reporting by customizing it to the needs of each trial.

The last set of articles focuses back on one of the fundamental features of effectiveness trials, namely the embrace of the heterogeneity of patients seeking treatment in the community and the importance of exploring this heterogeneity, how it may moderate the effects of treatments, and how it may help guide the future design of treatments. Nunes et al. (25) argue the importance of covariation for baseline severity level of the outcome measure and testing the baseline severity by treatment interaction in primary outcome analyses testing treatment effects and describe an analytic framework for doing so. Hillhouse et al. (26) describe the variability in dose of buprenorphine achieved among opioid-dependent patients during a flexible dose titration phase of a clinical trial and its relationship to other patient features. Hartzler et al. (27) examine stimulant users drawn from CTN trials, showing that those with comorbid alcohol use disorders have greater severity and psychiatric comorbidity. Finally, the article of the late Malcolm Reid (28), to whose memory this Special Issue is dedicated, examines demographic and clinical features predicting likelihood of achieving abstinence from smoking in the trial that he led in the CTN, testing nicotine patch plus counseling for treatment of smoking among drug-dependent patients in treatment. Findings of lower likelihood of abstinence among older patients, African Americans, and patients with greater severity of nicotine dependence and of their primary substance problem suggest the importance of tailoring smoking cessations treatment to these subgroups and emphasis on more aggressive treatment of the primary substance problem.

As highlighted in Dr. Donovan's article (20), the design and implementation of a multisite effectiveness trial should be a bidirectional, collaborative process. One of the rewarding aspects of working on effectiveness research in CTN is the teamwork. Teams in the CTN have come together around each study, and special interests groups have formed around issues like HIV, gender, ethnicity, pharmacotherapy, behavioral therapy, and design and analysis that cut across trials. These teams include researchers, community-based providers, the sponsor (NIDA), and contractors providing data analysis, management, and quality assurance. Most of the articles included in our Special Issue are the product of one or more of these teams. Thanks are due to each of the teams that answered the Call for Papers; to the Journal Editor, Tom Kosten; and Managing Editor, Coreen Domingo; to Carrie Davies who managed production from my office; to NIDA for funding the CTN; and to Betty Tai and her team at the Center for the CTN at NIDA for their leadership of the CTN. Finally, special thanks are due to the many reviewers and especially to George Bigelow, Chair; Jack Blaine, Coordinator; and the members and reviewers of the Publications Committee of the CTN, who provided high-quality reviews for many of our articles.

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