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Clinical trials as treatment option: Bioethics and health care disparities in substance dependency☆

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ABSTRACT

Bioethicists have warned against the dangers of mixing research with treatment. They are concerned that research priorities may take precedence over individual patient needs and that research subjects tend to misunderstand the purpose of research or overestimate the direct medical benefits of participating in studies. Yet, other work has questioned whether clinical research can always be separated from therapeutic benefit for participants. Using in-depth interviews with participants in two phase III randomized U.S. clinical trials for methamphetamine dependency, we examine the treatment options available to participants, their experiences with participating in the trials, and potential problems of trial participation. We find that while participants have experience with four alternative treatment modalities – quitting alone, support groups, in-patient treatment facilities, and consulting primary care physicians – the randomized clinical trials compare favorably to alternatives because they provide access to evidence-based behavioral treatments, specialized medical professionals, non-judgmental staff, and the possibility of receiving an experimental drug. We conclude that while randomized clinical trials are imperfect substitutes for clinical care, they constitute a fragile and sporadic therapeutic niche in a country with fundamental problems in access to health care, a mixed punitive-therapeutic drug addiction policy, and a profit-driven pharmaceutical development and approval process.

In contrast to medical researchers' tremendous investment in randomized controlled trials (RCTs) as the elementary building blocks of evidence-based medicine, social scientists have critically assessed the epistemic and political characteristics of trials (see, for example Abraham, 2007; Cartwright, 2007; Fisher, 2008; Fishman, 2004; Grossman & MacKenzie, 2005; Lakoff, 2005; Orr, 2006; Sismondo, 2008; Worrall, 2002). While the risks of trial participation are well covered in the social science literature and the merits of the knowledge gained from trials have been parsed out in detail, opinions diverge about the extent to which RCTs directly benefit population health in the U.S. Most observers agree that clinical trials intend to produce knowledge for future patient populations, but the risks and therapeutic benefits for current trial participants remain contested. Bioethicists have cautioned that mixing research with treatment risks the "therapeutic misconception," defined in a consensus statement as a lack of understanding of the defining purpose of clinical research to produce generalizable knowledge regardless of any benefits subjects may derive from participating in the trial (Henderson et al., 2007, p. 1736). We argue that concerns about individuals' therapeutic misconception in trials need to be assessed against available health care alternatives. In countries marred by deep-seated health disparities trials may offer, albeit sporadically, some of the highest quality care available.

Bioethicists and policy makers acknowledge that participating in trials may present rare access to potentially lifesaving therapies, and therefore the benefits of participation need to be equally distributed among the population (Pace, Miller, & Danis, 2003). Throughout the 1980s, RCTs were one of few treatment options for people with AIDS, providing access to AZT and other experimental antiretroviral drugs (Epstein, 1996). For many, however, access to such drugs remained limited by slow drug approval processes and trial design. Under a new policy (NIH Revitalization Act, 1993), clinical trials were charged with including women, racial and ethnic minorities, children, and the elderly in clinical research and measuring different treatment responses for these subpopulations. Steven Epstein (2007) has documented the ascent of this "inclusion-and-difference" paradigm in health policy as a regulatory correction to the drug industry's tendency to restrict trial participation to middle-aged white males. Although immediately concerned with the generalizability of treatments, these policy

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activities presume that participation in RCTs produces therapeutic benefits that should be accessible to all.

Despite these implied therapeutic benefits for patient populations, bioethicists have warned against mixing clinical research and health care, arguing that physicians and nurses who also work as researchers generate an inherently coercive and exploitative situation (Katz, 1993). In contrast to the diagnostic procedures and individualized treatments medical providers offer patients, biomedical researchers expose subjects to uncertain risks in order to create generalizable scientific knowledge for future generations of patients. According to bioethicists these two orientations are fundamentally at odds: when patients participate in trials, some decisions – e.g., about treatment regimens, drug dosages, and biological sample collection – may pose risks that are not balanced by benefits for individual patients (Miller & Brody, 2002). As part of the RCT protocol, researchers may also expose research subjects to invasive procedures that have little therapeutic merit. For research subjects, the result may be a "therapeutic misconception," where research subjects misunderstand the purpose of research and scientific inquiry or aspects of the research protocol – e.g., randomization or the administration of a placebo – (Henderson et al., 2007) and overestimate the direct medical benefit of participating in studies (Appelbaum, Roth, & Lidz, 1982; de Melo-Martin & Ho, 2008). A number of studies have documented some level of therapeutic misconception among research participants (see Kimmelman, 2007). Conflating research with clinical care – and subjects with patients – may occur among both subjects and clinical investigators (Joffe, Cook, Cleary, Clark, & Weeks, 2001) and threatens the validity of informed consent, protection of human subjects, and research integrity (Miller & Rosentstein, 2003).

Whether subjects understand that the purpose of clinical research is to produce generalizable knowledge, trial participation may potentially produce direct and indirect therapeutic benefits. In a meta-review, Braunholtz and colleagues (Braunholtz, Edwards, & Lilford, 2001) show evidence that RCTs are more likely beneficial than harmful for participants; however insufficient data and the lack of appropriate non-trial comparison groups are cited by the authors (p. 223), as a limitation to the evaluation of the effect of trial participation on subject outcomes. In their meta-review, Peppercorn, Weeks, Cook, and Joffe (2004) find inconclusive evidence that trial participation has a direct therapeutic benefit and propose several alternative explanations for observed trial effects that are not adequately controlled for in other studies. Despite the lack of clear evidence of direct therapeutic benefit from trial participation, subjects may receive a number of indirect benefits through participation, including additional non-trial treatments and clinical care – referred to as "collateral" benefits (King, 2000, p. 333). Patients who play a dual role as research subjects perceive many kinds of "care" in their interactions with researchers. These relationships with researchers are more appreciated than those with traditional health care providers due to increased time commitments and personalized attention (Easter, Henderson, Davis, Churchill, & King, 2006). Given these benefits, researchers have questioned whether clinical research can and should be separated from therapeutic benefit for participants and the extent to which trials provide an appropriate therapeutic option for participants (Henderson et al., 2007).

These discussions about the therapeutic benefits and misconception of RCTs presume that high-quality medical care is available outside research settings. Yet, an extensive body of epidemiological and health services research has convincingly documented that access to health care and the quality of services in the U.S. varies extensively by geography and demography (e.g., Fisher, Goodman, Skinner, & Wennberg, 2008). Any evaluation of therapeutic benefits in trials should thus take the options for health care outside the trial into consideration. Furthermore, in countries such as the Czech Republic and Poland drug trials have become default options for health care delivery (Petryna, 2006).

At stake in the diverging perspectives about clinical research is the therapeutic benefit of RCTs for the approximately 4 million participants in 41,000 trials in the U.S.[1] In this article, we offer an empirical check on the bioethical position by taking the perspective of people looking for care and examining how RCTs compare to other available treatment options. We argue that for the patients facing health care decisions, bioethical dilemmas are structurally generated in a system rife with health disparities (see also (Anspach, 1993; Chambliss, 1996). We draw from two small phase III clinical trials of pharmacological treatments for methamphetamine dependency. Methamphetamine has been used in medicine for eighty years but legitimate indications are now limited. The drug is currently mainly prescribed as a short-term appetite suppressant or narcoleptic agent and occasionally as a treatment for hyper-activity disorder (unmethylated amphetamine is more commonly prescribed for ADHD). Methamphetamine remains a widely available psychostimulant used illicitly throughout the United States. Economists estimate that methamphetamine's economic burden in the U.S. amounts to between $16.2 and $48.3 billion (Nicosia, Pacula, Kilmer, Lundberg, & Chiesa, 2009). Methamphetamine is addictive and prolonged use may lead to paranoia and delusions, hypertension, heart damage, strokes, and deteriorating dental health (Barr et al., 2006). Quitting methamphetamine may lead to withdrawal symptoms such as drug cravings, anhedonia, and excessive sleeping (Winslow, Voorhees, & Pehl, 2007). While methamphetamine addiction is analogous to many chronic conditions, it is often treated as an acute illness and care provisions remain insufficient (McLellan, Lewis, O'Brien, & Kleber, 2000). We analyze the experience of trial participants not to suggest a general pattern of trial utilization in the U.S. but to highlight an underappreciated function of RCTs in a country with widespread access problems to quality health care.

Methodology

Our data are drawn from an explorative, observational study of two RCTs conducted in California to test the effectiveness of off-label use of an FDA-approved drug versus a placebo for treatment of methamphetamine dependency. The same research group conducted the two trials and followed a similar protocol. The first trial tested Bupropion, a norepinephrine and dopamine reuptake inhibitor of the aminoketone class that has been approved by the FDA as an antidepressant and as a smoking cessation drug. The second trial tested Modafinil, a non-amphetamine type stimulant that acts as a wakefulness-promoting drug, and has been approved by the FDA for managing symptoms of narcolepsy. Individuals were eligible to participate in the trial if they were at least 18 years old and met the DSM criteria for methamphetamine dependency. Besides administration of Bupropion/Modafinil or a placebo, the trials required thrice weekly urine samples for twelve-weeks, and offered an opportunity for cognitive-behavioral therapy and contingency management. The staff also collected a battery of cognitive tests and outcome data. Each trial aimed to enroll 70 research subjects total from two research sites.

We observed and interviewed the staff and trial participants over a one-year period between June 2006–2007. We interviewed all available staff members during this period ($N = 10$) about their tasks, motivation, challenges, and expectations for the trial on an

[1] These figures come from Thomson CenterWatch, E-mail communication, Mary Jo Lamberti, October 19, 2007.