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# Integrated Management of Physician-delivered Alcohol Care for Tuberculosis Patients (IMPACT): Design and Implementation

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## Abstract

**Background—**While the integration of alcohol screening, treatment and referral in primary care and other medical settings in the U.S. and world-wide has been recognized as a key health care priority, it is not routinely done. In spite of the high co-occurrence and excess mortality associated with alcohol use disorders (AUDs) among individuals with tuberculosis (TB), there are no studies evaluating effectiveness of integrating alcohol care into routine treatment for this disorder.

**Methods—**We designed and implemented a randomized controlled trial (RCT) to determine the effectiveness of integrating pharmacotherapy and behavioral treatments for AUDs into routine medical care for TB in the Tomsk Oblast Tuberculosis Service (TOTBS) in Tomsk, Russia. Eligible patients are diagnosed with alcohol abuse or dependence, are newly diagnosed with TB and initiating treatment in the TOTBS with Directly Observed Therapy-Short Course (DOTS) for TB. Utilizing a factorial design, the Integrated Management of Physician-delivered Alcohol Care for Tuberculosis Patients (IMPACT) study randomizes eligible patients who sign informed consent into one of four study arms: (1) Oral Naltrexone + Brief Behavioral Compliance Enhancement Therapy (BBCET) + treatment as usual (TAU), (2) Brief Counseling Intervention (BCI) + TAU, (3) Naltrexone + BBCET + BCI + TAU, or (4) TAU alone.

**Results—**Utilizing an iterative, collaborative approach, a multi-disciplinary U.S. and Russian team has implemented a model of alcohol management that is culturally appropriate to the patient and TB physician community in Russia. Implementation to date has achieved the integration of routine alcohol screening into TB care in Tomsk; an ethnographic assessment of knowledge, attitudes and practices of AUD management among TB physicians in Tomsk; translation and cultural adaptation of the BCI to Russia and the TB setting; and training and certification of TB physicians to deliver

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oral naltrexone and brief counseling interventions for alcohol abuse and dependence as part of routine TB care. The study is successfully enrolling eligible subjects in the RCT to evaluate the relationship of integrating effective pharmacotherapy and brief behavioral intervention on TB and alcohol outcomes, as well as reduction in HIV risk behaviors.

**Conclusions—**The IMPACT study utilizes an innovative approach to adapt two effective therapies for treatment of alcohol use disorders to the TB clinical services setting in the Tomsk Oblast, Siberia, Russia and to train TB physicians to deliver state of the art alcohol pharmacotherapy and behavioral treatments as an integrated part of routine TB care. The proposed treatment strategy could be applied elsewhere in Russia and in other settings where TB control is jeopardized by AUDs. If demonstrated to be effective, this model of integrating alcohol interventions into routine TB care has the potential for expanded applicability to other chronic co-occurring infectious and other medical conditions seen in medical care settings.

### Keywords

Alcohol use disorders; treatment; tuberculosis; naltrexone; brief counseling intervention

## Background and Rationale

The integration of alcohol screening, treatment and referral in primary care in the U.S. and world-wide has been recognized as a key health care priority (Babor et al., 2007; Fleming et al., 1998; Hasin et al., 2007; Mannelli and Pae, 2007). In one study of 19,000 U.S. adults seen in primary care practices, the prevalence of at-risk drinking ranged from 7.5% to 19.7% (Fleming et al., 1998). Nevertheless, in a sample of primary care practices across the United States, only 24% primary care patients were screened for alcohol use disorders, and of those with an alcohol problem, only 30% received any counseling (Hasin et al., 2007). Similar prevalence rates of alcohol problems in primary care are seen in Europe (Alonso et al., 2004; Rehm and O'Hara, 1985) and other countries (Rehm and O'Hara, 1985; World Health Organization, 2004). In certain regions of the world, the prevalence of alcohol use disorders is, comparatively, even higher and growing(Melchior et al., 2008; Pomerleau and Adkins, 1980). Unfortunately, in many such settings, the enormous public health implications of alcohol use disorders (AUDs) – in terms of direct medical and social consequences and indirect effects on other medical disorders – are barely recognized, much less addressed.

In this sense, the failure to integrate alcohol treatment into the primary care of populations that suffer from AUDs and co-occurring medical problems represents a missed opportunity with serious clinical and public health implications (Willenbring, 2005). The pathologic synergy between AUDs and other chronic medical conditions has been well-described (Mannelli and Pae, 2007; Meulemans et al., 2002a; Meulemans et al., 2002b). In particular, for diseases of poverty, such as HIV/AIDS and tuberculosis (TB), AUDs place individuals at increased risk of acquiring the disease and, once infected, experiencing greater morbidity and mortality (Marcellin et al., 2008; Miguez et al., 2003; Peters and Terrault, 2002; Stevens, 2004) Both biological and psychosocial mechanisms explain the impact of AUDs on developing and succumbing to these diseases (Braithwaite et al., 2007; Brudney and Dobkin, 1991; Burman and Escarce, 1999; Dossing et al., 1996; Fernandez-Villar et al., 2004; Kucherov, 1990; McDonnell et al., 2001; Nijhawan et al., 2008; Razvodovskii Iu, 2004; Zhamborov, 1999).

In the case of TB, AUDs interact in multiple ways. The cell-mediated immunosuppressive effect of alcohol is well-recognized although poorly understood (Nelson et al., 1995). Alcohol hepatitis may also complicate TB treatment since several antituberculosis agents are potent hepatotoxins (Dossing et al., 1996; Fernandez-Villar et al., 2004). Individuals with AUDS are more likely to be nonadherent to TB therapy, thus increasing their risk of treatment failure, treatment interruption, and death (Brudney and Dobkin, 1991; Burman and Escarce, 1999;

McDonnell et al., 2001; Pablos-Mendez et al., 1997). Recent studies conducted in Russia and Eastern Europe identified alcohol abuse as the single strongest risk factor for TB treatment interruption (Belilovskiy, 2005; Gelmanova et al., 2007). AUDs have been associated with drug-resistant TB in multiple countries, including Russia (Pablos-Mendez et al., 1997; Toungoussova et al., 2002). Finally, for individuals living in poverty – be it in marginalized segments of the United States or in shanty-towns in a lower income country – suffering from AUDs and chronic medical illness further contributes to a cycle of poverty, displacement and socioeconomic disempowerment that often makes recovery unattainable, even for the most motivated.

These inherent challenges of treating patients with co-occurring medical and alcohol use disorders also represent unique opportunities for effective, integrated care. First, individuals who receive care for medical conditions could be motivated to modify their alcohol use behavior. By linking alcohol intake with negative outcomes of their co-occurring condition, some patients may be more likely to engage in alcohol harm reduction as part of management efforts to improve outcomes related to other health problems. Second, at the global level, national programs to treat endemic diseases such as TB and HIV/AIDS could provide the infrastructure to deliver alcohol care in settings where specialized alcohol treatment services are almost nonexistent in the public sector. For example, an ideal infrastructure for delivering integrated alcohol care is “DOTS” (directly observed therapy, short-course), a TB management strategy endorsed by the WHO that is based on five principles: political commitment with increased and sustained financing; case detection using quality-assured bacteriology; standardized treatment with direct supervision and patient support; an effective drug supply and management system; and monitoring and evaluation with impact measurement (Chaulk and Kazandjian, 1998; Chaulk et al., 1995; Volmink et al., 2000; World Health Organization, 2005). DOTS is currently implemented in 184 countries that account for 99% of all estimated TB cases, including 4.9 million new cases of TB identified in 2006 and a treatment success rate of 84.7% in 2005 (World Health Organization, 2008). Given an estimated 9.2 million new cases of TB and 14.4 million prevalence cases in 2006, DOTS has had an enormous global public health impact by successfully detecting and treating TB in the most impoverished and high-burdened countries. Because TB disproportionately affects the most marginalized social strata, DOTS includes direct supervision of therapy and additional patient support (e.g. treatment adherence incentives, active outreach to minimize treatment nonadherence and default); these rigorous case-holding strategies create an ideal opportunity to deliver alcohol care to some of the most inaccessible populations.

Yet, in spite of the high co-occurrence and excess mortality associated with AUDs among individuals with TB (Razvodovskii Iu, 2004; Zhamborov, 1999), HIV (Braithwaite et al., 2007; Nijhawan et al., 2008), and other diseases of poverty (Marcellin et al., 2008; Peters and Terrault, 2002), to our knowledge, only one randomized clinical trial has tested the effectiveness of integrating alcohol treatment into the routine delivery of care for such conditions (Parsons et al., 2007). In addition, efficacious pharmacotherapies for alcohol use disorders are not widely available in many resource-poor settings (Phillips et al., 2003). Moreover, individual behavioral therapies for alcohol use disorders are not often used in general medical or specialty care settings. To our knowledge, there are no studies of effectiveness of physician use of brief counseling interventions or motivational interviewing for reducing drinking in resource-poor settings. To address this gap, we are currently conducting a randomized controlled trial to deliver integrated alcohol care to patients with tuberculosis in Tomsk, Siberia, the Integrated Management of Physician-delivered Alcohol Care for Tuberculosis patients (IMPACT) Study. The study has two innovative features: (1) to adapt two effective therapies for treatment of alcohol use disorders to the TB clinical services setting in the Tomsk Oblast, Siberia, Russia and (2) to train TB physicians to deliver state of the art alcohol pharmacotherapy and behavioral treatments as an integrated part of routine TB

care. In this manuscript, we will describe the concept, rationale, and study design of the IMPACT study.

## Study Aims

The IMPACT trial (Integrated Management of Physician-delivered Alcohol Care for Tuberculosis patients) is a randomized controlled trial to assess the effectiveness of two alcohol interventions administered singly or in combination as an integrated component of TB care provided to patients with co-occurring TB and AUDs in Tomsk, Russia. Consenting patients who are starting TB treatment and are diagnosed with an AUD are randomized to one of the four following study arms: (1) A Behavioral Counseling Intervention (BCI) plus treatment as usual (TAU) (i.e. standard referral to and management by an addictions specialist); (2) Pharmacotherapy with oral naltrexone plus Brief Behavioral Compliance Enhancement Therapy (BBCET) plus treatment as usual; (3) Behavioral Counseling Intervention plus oral naltrexone plus BBCET plus treatment as usual; and (4) Treatment as usual alone.

An important aspect of the delivery of these alcohol interventions is their incorporation into routine TB care and delivery by non-alcohol specialists (i.e. TB physicians). In this study, we exploit the strengths of the TB care delivery paradigm (DOTS) by linking to this care system the provision of alcohol interventions. To this end, we have incorporated the following innovative approaches to AUD management among TB patients:

1. The Behavioral Counseling Intervention (BCI) has been adapted through iterative collaboration of an interdisciplinary team of local and international specialists to derive a protocol that is easily integrated into routine patient care by TB physicians. This process includes an assessment for feasibility and cultural acceptability of the interventions within the Tomsk clinic and ongoing fidelity monitoring and supervision of TB physicians for adherence to the BCI protocol.
2. Naltrexone is delivered in the context of DOTS, administered under direct observation administration along with TB medications.
3. We have adapted and incorporated BBCET as the brief medical management that accompanies sessions during which naltrexone is prescribed and monitored. In contrast to the BCI and with the specific goal of enhancing patient compliance to naltrexone, the BBCET consists of brief (1–5 minute) sessions during which physicians and patients can discuss adverse effects, medication compliance and treatment goals. Its emphasis is on the pharmacotherapy, and none of the BCI strategies are used during these sessions.

The primary endpoints of the study are (1) successful TB response, classified per WHO as cured or treatment completed (versus treatment failure, defaulted, died or transferred out to another health facility) (World Health Organization, 2005); (2) change in mean number of heavy drinking days in last month of study period compared with baseline, as measured by the Time Line Follow Back (TLFB) method (Sobell et al., 1992) and (3) HIV risk behavior, defined as the change in mean score of the Risk Assessment Battery (Navaline et al., 1994). Because we hypothesize that greater decrease in overall alcohol consumption will be associated with improved TB outcomes and decreased HIV risk behavior, the primary outcome measure, change in the mean number of heavy drinking days, was chosen to detect changes in overall consumption and not just abstinence. Secondary outcome measures include change in mean number of drinks per drinking day and change in Addiction Severity Index (McLellan et al., 1992) alcohol composite scores. Our group has used these primary and secondary outcome measures in previous studies (Greenfield et al., 2007; Greenfield et al., 1998; Weiss et al., 2007).

We aim to test the following hypotheses: Individuals receiving one of the three interventions (Naltrexone +BBCET+TAU, BCI+TAU or the combination therapy) will experience better TB outcomes and a greater change in the mean number of heavy drinking days, compared with the individuals receiving TAU only. Finally, we hypothesize that a decrease in alcohol consumption will be associated with decreased HIV risk behavior.

## Study Setting

We chose Tomsk, Russia as the site for this clinical trial because of the heavy burden of AUDs and TB in the Russian population. Currently, Russia has the greatest estimated consumption of alcohol per capita in the world (Cockerham et al., 2002; Nemtsov, 2000). Alcohol consumption has contributed to the marked increase in mortality and decline in general health in Russia over the past several decades. Higher levels of alcohol consumption have been associated with worse self-rated health (Bobak et al., 1999) and unintentional alcohol poisoning in men has increased from 57.6 per 100,000 in 1998 to 90.2 per 100,000 in 2001 (Men et al., 2003). Between 1991 and 2001, there has been an increase in overall mortality in Russia, with life expectancy among men falling from 63.5 years to 58.9 years (Men et al., 2003). Alcohol has been cited as the most important underlying factor driving Russian mortality and is thought to play a major role in deaths from multiple causes including suicides, homicides, cardiovascular disease, and TB (Chenet et al., 1998; Chervyakov et al., 2002; Kherosheva et al., 2003; McKee et al., 2001; Medvedev et al., 2003; Ryan, 1995; World Bank, 2005).

TB has also emerged as a major health problem in Russia and is now the leading infectious cause of death in Russia. The TB problem in Russia is further compounded by the fact that rates of multidrug-resistant TB (MDR-TB) are among the highest in the world (World Health Organization, 2008). Despite intense efforts at controlling the spread of the disease (Kherosheva et al., 2003; Mawer et al., 2001; Orellana, 2002), rates of TB and MDR-TB continue to rise, in part due to increased vulnerability from socioeconomic pressures and certain co-occurring disorders such as AUDs. The Russian Federation began using the DOTS approach in pilot projects in 1996 and is now expanding DOTS coverage throughout the nation.

Tomsk Oblast is representative of these national trends in AUDs and TB. Tomsk is located in western Siberia, with a population of 1,040,000 in an area the approximate size of Poland; approximately half reside in Tomsk City. In 2003, TB incidence in Tomsk was 93.4 per 100,000. TB mortality was 17.7 per 100,000 persons that year, compared with a national rate of 21.9 deaths per 100,000 inhabitants from all causes. In that year, there were 800 new and 100 re-treatment cases (Mathew et al., 2009) in Tomsk. We have found that AUDs in this population are common with 50% of all TB patients meeting criteria for lifetime alcohol dependence or abuse per Diagnostic and Statistical Manual Fourth Edition (DSM-IV) (American Psychiatric Association, 1994) as measured by the Composite International Diagnostic Interview-Substance Abuse Module (CIDI-SAM) (Mathew et al., in press; Medvedev et al., 2003; World Health Organization, 1993).

## Study Treatments

### General Principles for Treatment Selection

There are a number of cultural and organizational barriers in Russia to the integration of alcohol treatment within medical settings (Fleming, 1996; Fleming et al., 1994; Medvedev et al., 2003). Many patients within medical settings who have co-occurring AUDs are in either a precontemplative or contemplative stage of change (Prochaska et al., 1992), and this holds true for the population receiving treatment in the Tomsk TB services. Pre-contemplation is noted in patients who do not convey any intention to change their behavior in the foreseeable future; in contrast, contemplative patients are aware of their problem and are considering steps without

commitment (Prochaska and Norcross, 2001). Instruction as to how to recognize these stages and deliver the appropriate interventions was included in training sessions for all study physicians. For patients within the Russian medical system, referral for alcohol treatment requires registration and may have an impact on employment status (Fleming et al., 1994; Mathew et al., in press) This enhances stigma and decreases the likelihood that an individual with drinking problems will receive treatment. Another specific barrier to engaging those who may be ambivalent about receiving alcohol treatment, includes a more physician-centered, hierarchical medical system in Russia, rather than a patient-centered approach that has been demonstrated to be more effective in engaging ambivalent patients and enhancing behavioral change (Fleming et al., 1994; Lichterman, 2005). Behavioral treatments are not a routine part of alcohol treatment in Russia in general and in primary care specifically. On the other hand, because these highly effective treatments were not widely available due to lack of training of physicians in primary medical settings, this represented a novel approach which we felt could be adapted to be culturally appropriate.

Therefore, the basic principles for selection of therapies for this study were (1) prior demonstrated effectiveness in primary medical settings, (2) potential for acceptability in the Russian medical setting for both physicians and patients, (3) ability to deliver interventions in rural and urban, outpatient and inpatient settings requiring flexibility within the chosen intervention, and (3) potential for appropriate cultural adaptation.

### Specific Concerns for the Selection of the Pharmacotherapy

While pharmacotherapy of medical illness is acceptable among both physicians and patients in the Russian medical system, pharmacologic options for alcohol dependence are only administered by a narcologist (e.g., addiction specialist) and not in the general medical setting. At the inception of this study, the only pharmacotherapy for alcohol dependence widely in use in Russia was disulfiram. Another approach widely in use in Russia has been “coding” a form of aversive therapy in which the patient undergoes placebo surgery, is then given alcohol to drink after which the patient is injected with calcium chloride or magnesium sulfate to produce an unpleasant sensation; the patient is told that any subsequent alcohol intake will trigger a more severe reaction due to the surgical implant (Entin, 1990; Mathew et al., in press). We perceived that the likely effectiveness and acceptability of widespread disulfiram or coding integrated into TB care would be low. On the other hand, oral naltrexone was approved for alcohol dependence in Russia, but was not widely used due to prohibitive cost.

The efficacy of naltrexone in treating alcohol abuse and dependence has been established. Naltrexone is an opioid antagonist which decreases the pleasurable response to and craving for alcohol consumption (Littleton and Zieglgansberger, 2003). While several clinical trials have failed to demonstrate the efficacy of naltrexone compared with placebo (Ahmadi and Ahmadi, 2002; Chick et al., 2000; Heinala et al., 2001; Kranzler et al., 2000; Krystal et al., 2001), many more randomized controlled trials and several meta-analyses have shown naltrexone to be efficacious in preventing relapse, reducing alcohol intake and maintaining abstinence (Adinoff et al., 2005; Anton et al., 2006; Bouza et al., 2004; Kessler et al., 2001; Kranzler and Van Kirk, 2001; Monti et al., 2001; Morris et al., 2001; O’Malley et al., 1992; Srisurapanont and Jarusuraisin, 2005a; Srisurapanont and Jarusuraisin, 2005b; Streeton and Whelan, 2001; Volpicelli et al., 1992). Treatment with naltrexone has also been associated with increased study drug adherence compared with placebo in some meta-analyses (Srisurapanont and Jarusuraisin, 2005b), although not in others (Bouza et al., 2004). Most of these clinical trials have excluded individuals with serious medical conditions (e.g. TB); therefore, it is important to ascertain its effectiveness among TB patients with co-occurring AUDs. Therefore, we designed this intervention to be open-label, instead of placebo controlled. The purpose of this study is not to demonstrate its efficacy but rather to assess relative effectiveness when

implemented as part of routine TB care in patients with co-occurring TB and AUDS in comparison to the current standard of care for alcohol management in this setting.

Because naltrexone is an evidence-based pharmacotherapy of alcohol dependence that could be easily integrated in the primary care medical setting, and represented a new treatment, we anticipated that it would generate interest and be acceptable to both TB physicians and patients. It also would not have the potentially negative perceptions that might be associated with disulfiram given the history of its use as a treatment for alcohol dependence in Russia. We examined potential interactions and concerns with liver toxicity for naltrexone in combination with rifampin and other anti-tuberculous drugs, but did not find this was a significant concern as long as liver function tests were monitored (Peloquin, 2005).

Prior pharmacotherapy trials for alcohol dependence have administered medication with some type of medical management in which physician and patient briefly discuss adverse effects, medication compliance and overall goals of treatment (Anton et al., 2006; COMBINE Study Research Group, 2003; Johnson et al., 2007; Project MATCH Research Group, 1997). Because the efficacy of the medication has been the primary target of investigation (Anton et al., 2006), and because the potency of behavioral interventions has been demonstrated, these interventions have been brief in duration (e.g. 1–5 minutes) (Johnson et al., 2007). We selected the Brief Behavioral Compliance Enhancement Therapy (BBCET) intervention that was developed for a multisite trial of topiramate for alcohol dependence (Johnson et al., 2003). In collaboration with the authors of the manual for this intervention, we adapted this for the specific aims of this study including the Russian setting, and administration to patients with co-occurring TB and alcohol dependence. The treatment manual organizes sessions according to three phases of treatment: 1) initiation of treatment, 2) maintaining the patient's commitment to treatment, and 3) phasing out the medication and terminating treatment. Sessions are limited to topics related to naltrexone medication, including adverse events, adherence, and goals specific to naltrexone treatment. After we adapted this treatment manual, it was translated into Russian and evaluated for cultural appropriateness by our Russian colleagues, comprised of alcohol and TB physicians.

In order to integrate the pharmacologic intervention into TB services, we decided to deliver naltrexone (50 mg per day) under directly observed therapy (DOT) for TB. The TB provider responsible for directly supervising the administration of TB drugs (usually a nurse who works at the clinic/hospital) administers the naltrexone, at the same time as antituberculosis medications. This occurs at one of the three treatment sites or else in home-based therapy, as per TB services. Since DOT for TB treatment does not routinely occur on Sunday, patients are given a dose of naltrexone on Saturday for self-administration on Sunday, and self-reported adherence is verified and recorded on the following Monday. We created a naltrexone treatment administration card that mimics the form used to document DOT of TB treatment. DOT supervisors have found this card easy to fill out along with the TB treatment card. In deciding on the duration of naltrexone for this trial, we considered prior clinical trial experiences. The majority of clinical trials have administered naltrexone for 12 weeks, and few assess the impact beyond 6 months of treatment. The benefits of a 12-week course of naltrexone appear to disappear within six months from the time of discontinuation (Anton et al., 2001; Bouza et al., 2004; Monti et al., 2001; O'Malley et al., 1992). Treatment with naltrexone for longer durations (ranging from six to 24 months) has been explored in several trials (Alling et al., 1982; Balldin et al., 2003; Heinala et al., 2001; Knox and Donovan, 1999; Krystal et al., 2001; Landabaso, 1999; Rubio-Stipec et al., 1991; Volpicelli et al., 2000). Although one study failed to demonstrate efficacy of naltrexone administered for 12 months (Krystal et al., 2001), other trials show a favorable effect on reducing alcohol consumption throughout the course of treatment, without elevated rates of toxicity (Alling et al., 1982; Balldin et al., 2003; Garbutt et al., 2005; Landabaso, 1999). Based on these data, we felt that a longer duration of naltrexone

would likely maximize treatment effect and posed little additional risk of toxicity; therefore, we decided to provide naltrexone for the duration of standard first-line TB treatment, six months.

## Specific Concerns for the Selection of the Behavioral Interventions

Earlier work with the Tomsk TB Alcohol Working Group identified several characteristics of our target patient population as well as the physicians working in the TB services in Tomsk. Many patients receiving services for TB were in the pre-contemplative or contemplative state with regard to their drinking. Therefore, the chosen intervention would need to provide education about alcohol, emphasize the impact of alcohol on TB outcomes, and focus on TB cure as one of the primary goals of reducing alcohol consumption and ultimately achieving abstinence from alcohol.

Previous meta-analytic reviews have shown that brief interventions are more effective than control conditions (Effective Health Care Team, 1993; Poikolainen, 1999) and as effective as longer term care in reducing alcohol use and associated negative consequences (Bien et al., 1993; Moyer et al., 2002; Wilk et al., 1997). Additionally, studies have shown that brief alcohol interventions can be integrated into medical settings (Brady et al., 2002; Mcmanus et al., 2003), effectively delivered by physicians (Fleming et al., 1997; Reiff-Hekking et al., 2005), and improve medication and adherence to treatment for co-occurring medical problems (e.g., HIV, diabetes, hypertension) as well as reducing target alcohol symptoms (Fleming et al., 2004; Parsons et al., 2007). While Moyer et al. (Moyer et al., 2002) suggests that brief interventions are most effective when applied to individuals who are not drinking excessively (Heather, 2002; Wilk et al., 1997), others note that brief interventions are effective even among excessive drinkers (Heather, 2002; Lieber et al., 2003). Further, the WHO's Brief Intervention Study Group found that brief interventions reduced drinking outcomes among heavy drinkers in Moscow (WHO Brief Intervention Study Group, 1996). These findings suggest that brief interventions can improve alcohol and medical outcomes, even in heavy drinkers in Russia. Given these considerations, we chose to implement the behavioral counseling intervention utilizing a brief counseling intervention (Whitlock et al., 2002) and to train physicians to adopt a motivational interviewing style.

In this study, we chose to use the guidelines developed by the National Institute on Alcohol Abuse and Alcoholism (NIAAA), *Helping Patients with Alcohol: A Health Practitioner's Guide* (National Institute on Alcohol Abuse and Alcoholism, 2004). In order to utilize this guide, we adapted it to the Tomsk setting by (a) translating it into Russian, (b) modifying for cultural appropriateness, and (c) adding language emphasizing that TB cure is one of the primary motivators to reduce and abstain from drinking. After iterative feedback from the Tomsk TB Alcohol Working Group, we derived a final version, which was translated into Russian. The end result was a brief counseling intervention (BCI) to be delivered by the TB physician as a 10–15 minute segment of the patient's monthly clinic visit (usually 30 minutes) for each of the first six monthly TB physician visits. In addition to the manual, we created BCI progress notes for TB physicians to fill out for each BCI encounter. Each progress note closes with a list of goals and the physician's assessment of the patient's readiness to change; at the next monthly encounter; these notes then provide the TB physician with a starting point for the follow-up BCI. Some examples of how we adapted the BCI to the Russian context and conveyed the intervention to Russian providers follow.

**The five "A's" of BCI—**The five "**A's construct"** (National Institute on Alcohol Abuse and Alcoholism, 2004) is a treatment heuristic developed by Whitlock et al. (2002) that incorporates components demonstrated to be the most effective in bringing about positive behavior change across a variety of risky behaviors (Whitlock et al., 2002). Drawing from Whitlock et al, the

NIAAA's clinician's guide identifies the five A's as the preferred method of brief intervention delivery (National Institute on Alcohol Abuse and Alcoholism, 2005). The five As are: **Ask about Alcohol Use, Assess, Advise, Assist**, and **Arrange for Follow-up**. We translated these A's into Russian as the cyrillic C's: Спрашивать; сравнивать; советовать and содействовать; способствовать.) These C's roughly translate to mean "Ask, Assimilate/compare (meaning to discuss ambivalence), Advise, Assist, and Aid/Facilitate follow-up."

**Using the tuberculosis illness episode to engage the patient—**The content of the BCI includes normative feedback on the patient's alcohol consumption, including encouraging the patient to reflect on how drinking may be impacting his or her health. We incorporated feedback on the relationship between alcohol and TB treatment as an important component of the intervention. Physicians provide general information on the negative consequences of AUDs on TB treatment outcomes and review the patient's laboratory tests (including liver function tests) and TB treatment adherence, exploring the association between drinking and the risk of unsuccessful TB treatment. Written information on the relationship between alcohol and tuberculosis, as well as alcohol and HIV risk, is also provided to the patient. The goals of reduced drinking are framed within the larger goal of TB cure, with ongoing feedback through the course of treatment to encourage the patient to continue with successful modifications or engage in deeper reflection among individuals who are doing poorly in their TB treatment and continue to drink.

**Conveying the spirit of motivational interviewing—**Motivational Interviewing (MI) represents a therapeutic style of counseling rather than a single intervention (Rollnick and Miller, 1995). Among problem drinkers, confrontation by a health care provider can be associated with increased alcohol consumption (Miller et al., 1993). Thus, the MI style is not confrontational; instead, patient-centered yet directive counseling encourages collaboration and assists the client in exploring his or her own ambivalence about behavior change. The transtheoretical model of readiness to change (Prochaska et al., 1992) and motivational interviewing (Burke et al., 2003; Dunn et al., 2001; Miller and Rollnick, 2004) were unfamiliar concepts to Russian physicians. In fact, the MI style was a departure from the hierarchical doctor-patient relationship traditional to the Russian medical system. Therefore, we had to engage physicians and motivate them to use MI as an alternative to the physician-centered model of care that is traditional in Russia. On the other hand, we felt that the authority and respect held by physicians could also provide additional 'leverage' as patients tended to accept physician counseling and feedback on alcohol intake. The key to training, then, was to exploit the positive attributes of the Russian patient-physician relationship but at the same time convey the spirit of MI to TB physicians in a way that they would both understand and "buy in" to this style of counseling. To this end, we created a training videotape which demonstrated a BCI delivered with and without MI. The video opened discussion on the merits of both styles of treatment. We followed with role-plays by participating physicians that were designed to practice MI on aspects as diverse as smoking cessation, exercise and alcohol consumption.

## Study Design

### Implementation of the AUDIT

As part of our collaborative efforts to improve TB-alcohol care in Tomsk, the Tomsk TB Services implemented the AUDIT as part of routine initial evaluation prior to starting TB treatment (Saunders et al., 1993). Patients complete the AUDIT as a written questionnaire prior to seeing the TB physician for initial intake. Since its implementation, at least 1,565 patients have completed the AUDIT questionnaire between 2005 and November 2008. In addition, we conducted a study to calibrate the AUDIT to the standard diagnoses of alcohol abuse and dependence according to DSM-IV as ascertained by the Composite International Diagnostic

Interview (CIDI) (World Health Organization, 1993). We confirmed that AUDIT performed acceptably in this population of Russian TB patients, and that the conventional cut-off score of ≥ 8 yielded acceptable sensitivity and specificity for identifying individuals at risk of AUDs (Mathew et al., in press).

## Recruitment Considerations

For the RCT, patients with an AUDIT score of ≥ 8 are referred by their providers for further evaluation of study eligibility. Those who agree are referred to a member of the study staff who explains the purpose of the study. Interested patients are first asked to consent to undergo further evaluation to determine eligibility, using the Composite International Diagnostic Interview (CIDI) and laboratory assessments. Those who are diagnosed with an Alcohol Use Disorder (AUD) (i.e., alcohol abuse or dependence) on the basis of CIDI-SAM scores and meet other inclusion and exclusion criteria are then approached for a second informed consent for RCT enrollment. In addition to a diagnosis of an AUD by CIDI, patients had to meet the following criteria: (1) diagnosed with TB and registered for TB therapy with the Tomsk Oblast Tuberculosis Services; (2) initiating TB treatment in one of the three study sites (inpatient hospital, polyclinic, day hospital). Potential participants were excluded from the study if they were under 18 years of age; had liver function tests more than three times the upper limit of normal range; reported opioid use in the past month or screened positive for opiates on urine toxicology screen; were pregnant or breastfeeding; demonstrated inadequate understanding of the study after undergoing informed consent; had any medical or psychiatric condition that made it impossible for them to comply with the study procedures; or had MDR-TB at the time of treatment initiation. Naltrexone will precipitate abrupt withdrawal from opioids (Anton et al, 2006); therefore, patients with a positive screen for opioids or past month use are excluded. The use of substances other than opiates is evaluated using the CIDI-SAM but is not part of the criteria for exclusion.

## Some Challenges and Solutions to Initial Recruitment for the Study

The initial phase of enrollment was slow and the study was not meeting its target; in the first five months of the study, we screened an average of nine patients per month and enrolled on average three, compared with a target enrollment of 12–15 per month. To overcome this obstacle, we explored physician and patient attitudes, asking for feedback from individuals who were proactive and those who were less supportive of the study. We identified the following barriers and then identified and implemented a number of solutions:

1. Physicians were concerned about the increased work burden. In response to this we increased physician compensation per study form and study intervention delivered; compensation increased to an approximate range of $4 (USD) to $10 (the previous range was $2 -$5).
2. Patients perceived little incentive to participate. We observed that once an initial group of patients enrolled in the study, receptivity of patients toward the study increased. This was especially true in the inpatient setting where study participants influenced group attitude. In addition, we increased patient compensation for participation, providing items ranging in approximate value from $5 to $7 (previous amounts ranged from $4-$6). Importantly, physicians objected to compensation with cash or items that could be sold for cash with which patients would buy alcohol; therefore, we finally selected a variety of appreciated necessities such as clothes, phone cards, among other items (Mathew et al., in press).
3. The enrollment process was complex and tedious, involving multiple steps including two informed consents, administration of the CIDI, and laboratory assessments. To facilitate this process, we identified a proactive physician at each site who worked as

'site coordinators' to navigate patients through the enrollment process. In addition, we dropped the AUDIT as the initial step for screening to recruit for the study and implemented the CIDI-SAM as the initial screening tool thus eliminating one step in the enrollment process. While the AUDIT performs well programmatically as a clinical screening tool, for the purpose of RCT enrollment, we felt that screening all patients with the CIDI (rather than those scoring ≥ 8 on the AUDIT) was justified in order to identify the maximum number of eligible individuals and accelerate study accrual.

Changes in compensation were discussed at length with the entire study team and were submitted for review by the appropriate ethics committees. While any compensation is inherently likely to influence enrollment and the nature of participation in the study, all parties determined that the total amounts and types of items were not coercive enough to significantly affect the outcomes. Additionally, compensation was altered in keeping with the fluctuations in the exchange rate between U.S. dollars and Russian roubles.

The solutions described above were implemented approximately 10 months into the study. Since these changes, we are screening on average nine patients per month and enrolling on average seven. Study staff is currently evaluating additional options to increase enrollment.

### Randomization procedure

The original RCT design stipulated that prior to study initiation, physicians would be randomly assigned to one of the four study arms and trained accordingly (e.g. BCI, NTX/BBCET plus BCI, NTX/BBCET alone, or treatment as usual). Once enrolled, subjects would be stratified by treatment site and undergo block randomization to receive one of the four possible interventions. Based on the intervention arm, the subject would then be assigned to one of the physicians at their treatment site who was trained in the designated study arm. The intent of this design was to increase the likelihood that the physician would maintain fidelity to the one treatment condition he/she was trained to implement. This design did not prove to be pragmatic. Tomsk TB services assign patients to physicians by geographic zones (e.g., physicians were to follow all TB patients living in a certain region of Tomsk); to adhere to the original study design would have substantially interfered with program conditions of TB services and therefore potentially have limited the generalizability of our study as a trial specifically seeking to understand whether these interventions would be effective under program conditions. Therefore, we trained all physicians to deliver treatment in all four arms of the study. Accordingly, we also increased our fidelity monitoring to minimize 'contamination.'

## Training

We conceptualized training the physicians for this RCT as a longitudinal process. First, we carried out several didactic lectures and question and answer sessions to provide an overview of the clinical trial and its objectives. U.S. physicians met with Russian physicians by teleconference and slides, didactic materials, and discussion were translated by a professional medical translator. Second, we provided teleconferenced and in-person training to the leaders of each TB treatment site. These sessions had the dual objectives of training the leading TB physicians in Tomsk and eliciting feedback to refine and finalize the interventions and general training curriculum. Finally, we conducted serial sessions with all TB physicians through both teleconferenced and in-person sessions, followed-up by one-on-one mock interviews on BCI and BBCET. Mock interviews were scripted for both training and certification, to provide consistent interviews for assessment. Since the study has been underway, we are conducting refresher trainings in the form of quarterly newsletters, teleconferenced discussions, and annual in-person refresher courses, responding to specific issues raised by physician participants from

the study experience. Below, we describe the design and delivery of training for each study intervention.

### Physician Training for Naltrexone and BBCET

For senior TB physicians, we initially conducted two 90-minute training sessions via teleconference as described above. Lectures reviewed the mechanism of action, pharmacology, administration and dosing, adverse effects and their management, as well as contraindications. Both sessions closed with a fully translated question and answer session period. In-person training of the entire group of TB physicians was subsequently carried out by the PI and project manager. In addition, training covered the BBCET, using methods as described below for the BCI. An additional list of questions and concerns raised by participants was compiled during the week-long training, which we then transmitted to the U.S. addiction specialist co-investigators; a written, consolidated "Q&A" hand-out with their responses was then distributed at the end of the week during a final teleconference with the U.S. addiction specialists at which any remaining questions were discussed. In addition, we developed simple flow-chart treatment algorithms for important management topics such as the management of naltrexone peri-operatively and the proper approach to common and life-threatening adverse events. We also provided translated literature on naltrexone, including a review of drug interactions with medications commonly used in TB management, e.g. codeine, dextromethorphan, etc.

### Physician Training for BCI

We developed the training materials for the BCI (and BBCET) by first creating didactic slides on the evidence base of BCIs, the trans-theoretical rationale of BCI and motivational interviewing, including stages of behavior change, and a description of the adapted BCI (including format, style, content). Then, we developed a role-playing session with a video-tape modeling three scenarios of BCI delivered with and without MI, . For the live role-playing session, physicians volunteered to play either the patient and provider, and received feedback using the "sandwich" method (positive comment, critical comment, and positive comment) to facilitate physician comfort, highlight target behaviors (e.g., reflexive listening) and non-MI-style behaviors (e.g., giving advice without first eliciting permission from the patient) (Poirier et al., 2004). The final phase of training involved a one-on-one mock interview performed by the project manager with each physician. Although time-intensive, this component of training was crucial to allow for feedback in a less threatening and individualized manner. If deemed necessary, the project manager conducted additional practice interviews until the physician felt comfortable to proceed with the certification interview.

Certification interviews involved a mock interview of the baseline and follow-up BCI and BBCET encounters which were reviewed by our fidelity assessment team. These interviews were tape-recorded and reviewed by a bilingual person trained in fidelity assessment, as described below. Based on assessment of the certification interview, the physician was certified for study participation or was required to repeat the certification interview. Eighteen (18) physicians completed the certification interview. Of these, all were successfully certified on the first round.

### Treatment Delivery Monitoring and Fidelity

**Monitoring fidelity to all behavioral interventions—**Monitoring interventions consists of assessing the performance of physician intervention delivery to ensure that both content and quality of the interventions do not drift from the protocol during the study. Fidelity assessment consists of documentation of patient encounter assessments, provision of feedback in a timely manner, and utilization of appropriate protocols in cases of inadequate performance. Since clinician skills with MI frequently deteriorate at two-to four-month follow-up post training

(Baer et al., 2004; Miller and Mount, 2001), we incorporated measures to assess BCI and BBCET adherence throughout the study. This fidelity monitoring was particularly important given that participating physicians delivered all four study arms, and ensuring against study "contamination" was crucial for internal validity. Therefore, the 3 aims of fidelity assessment were to 1) assess whether the behavioral interventions were appropriately delivered as per study protocol; 2) assess whether behavioral interventions were appropriately withheld per study protocol (e.g., those delivering BBCET only did not also receive BCI during the session); and 3) maintain adherence to behavioral interventions by providing ongoing feedback to study physicians based on the fidelity assessment. We developed a single fidelity assessment measure which allowed for evaluation of form, content and style for each of the BCI and BBCET (adapted from (Lane et al., 2005) interventions as well as a combined form for the BCI + BBCET intervention; additionally, a brief form for TAU was developed. These assessments are used to score physician fidelity to the behavioral intervention based on audiotaped recordings of sessions. For example, a physician delivering the BBCET/naltrexone intervention would have the session monitored to ensure that BBCET was properly executed and that BCI-specific interventions were avoided. We elected not to designate a cut-off score that would be considered "unacceptable" due to our aim in training the Russian physicians appropriately in novel treatment interventions. Instead, we opted to provide rapid feedback to physicians on their adherence to the behavioral intervention, positively reinforcing fidelity achieved and providing corrective feedback for deviations from protocol. Assessments in which form or content were not followed, or in which key components of style were applied "not at all" or "rarely" are considered problematic. Physicians with problematic performance are identified and subsequent measures to enhance fidelity are described below.

For this trial, one of the initial trainers and U.S. co-investigators trained two Russian-speaking research assistants (RAs) in adherence to the treatment conditions and the process of scoring physician tapes using the fidelity assessment forms described above. Each RA was certified by one of the US co-investigators, who reviewed translated transcripts of 10 certification interviews with the RA's assessments. Therefore, the certification interviews served the dual goal of certifying both the physicians and the RAs charged with coding tapes for fidelity. Calibration of coding among RAs occurs weekly with another US co-investigator who is the ongoing the fidelity supervisor.

It is standard practice for behavioral therapy trials to utilize ongoing monitoring of taped sessions using a standard instrument scored by a trained evaluator. . There was initial resistance by study physicians to audiotaping their behavioral sessions. The project manager worked with individual physicians to reinforce the study's need to assess fidelity to study interventions and thus ensure the integrity of study results. The individual attention increased physician acceptability to audiotaping sessions and sessions are now routinely audiotaped. Of the audiotaped interviews recorded, 10% of these are selected for transcription that are, in turn, assessed by the RAs. Feedback from the RA is conveyed to the physician during a meeting with the project coordinator, one week after the recording is reviewed. Any assessment that is deemed unacceptable or questionable, or for which there is any concern raised by the fidelity team are translated and then reviewed by a US co-investigator who is also blinded to the RA's initial assessment. Asesments are then discussed among the fidelity team, comprised of RAs, the project manager, and the U.S. co-investigator supervising the fidelity process.

Fidelity is assessed by uploading the digital audiorecording, along with the progress note for that encounter, onto a secure website, for review by one of the Russian speaking RAs. The interview is therefore reviewed in Russian and the coding assessment is done in Russian. The project manager reviews this coding assessment, and if necessary, discusses the assessment with the coding RA. The project manager is then responsible for reviewing this assessment

with the physician to provide feedback and enhance fidelity to the behavioral intervention being delivered.

Study physicians who are not adherent to the behavioral interventions receive detailed feedback and are invited to provide their perspectives on any difficulties they encounter in delivering the interventions. The study team provides suggestions for improvement and a specific performance improvement plan for the physician is then made. The physician can continue participation in the study, but monitoring is intensified as described above. If insufficient improvement is observed, the provider may be allowed to complete current cases, but no new subjects can be treated by that physician unless recertification occurs. Recertification involves the same process as described above. While these procedures are in place, no physician has yet required this level of intervention to bring treatment fidelity to an acceptable standard.

To date, we have recorded 16 (100%) physicians providing study encounters, and performed fidelity assessment of these encounters. We have provided feedback with an within one month on average. We have also identified common areas of greater difficulty in protocol adherence and addressed these with the group of study physicians in booster training sessions, highlighting clinical excerpts and providing corrective examples of delivering the intervention according to protocol. The cross-cultural challenges in training and fidelity assessment will be described more fully in a separate paper.

**Significance and Potential Contributions—**This model for alcohol care in the framework of treating co-occurring medical conditions is innovative and unique in several aspects.

1. This translational research seeks to implement evidence-based alcohol treatment interventions in a usual medical care setting, utilizing a well-established health care delivery model, DOTS. While clinical trials often optimize the subject population and treatment conditions, we seek to assess the impact of behavioral and pharmacologic alcohol interventions when carried out as part of routine TB care with minimal disruption to the environment of service delivery. If proven effective, such interventions will have been established through the study as part of TB care and will require few additional efforts to subsequently be adopted as routine management.
2. This study builds on a foundation established by a multi-disciplinary U.S. and Russian team of collaborators to develop a model of alcohol management that is culturally appropriate to the patient and TB physician community in Russia and now plans to assess its feasibility and effectiveness on TB and alcohol outcomes. This collaboration includes the integration of routine alcohol screening, using the Alcohol Use Disorders Identification Test (AUDIT) (Babor et al., 2001), into TB care in Tomsk as well as an ethnographic study to assess knowledge, attitudes and practices of AUD management among TB physicians in Tomsk (Mathew et al., 2008). Iterative dialogue and ongoing cultural assessment is incorporated into study practices as Russian and U.S. collaborators continue to overcome barriers both to study implementation and to alcohol care. Such collaboration recognizes the underlying factors of poverty and social instability driving the increase in AUDs and TB in Russian society and emphasizes development of study methods and a model of care that optimizes the feasibility of any implemented solutions in this doubly marginalized population.
3. A model of integrating alcohol interventions into the care of co-occurring medical conditions has the potential for expanded applicability to HIV infection and other chronic co-occurring medical conditions seen in usual medical care settings. While HIV risk behavior is measured as a study outcome, the intervention is primarily aimed at decreasing alcohol consumption, while directly addressing HIV risk behavior is

limited to providing an information sheet on alcohol use and HIV risk within the BCI protocol. Because we did not design the behavioral interventions to specifically address HIV risk, we hypothesize that a decrease in alcohol consumption (rather than the alcohol interventions themselves) will impact HIV risk. Our study thus provides an opportunity to better understand any indirect effects of alcohol interventions on HIV risk behavior in this population. If our hypotheses prove to be correct, the proposed treatment strategy could be applied elsewhere in Russia and in other settings where TB control is jeopardized by AUDs, including the United States (Brudney and Dobkin, 1991; Fleming et al., 1994; Pablos-Mendez et al., 1997). Furthermore, such a model of diagnosing and treating AUDs as an integral part of TB care could prove useful, possibly essential, in treating a variety of chronic medical co-occurring conditions among individuals with AUDs. For instance, the anticipated roll-out of highly active antiretroviral therapy (HAART) in Russia will need to address AUDs if effective adherence and virologic control is to be achieved. Thus, an effective strategy to identify and treat AUDs as part of routine TB care may have broader applicability in treating TB and other chronic diseases in Russia and elsewhere.

## Conclusions

To our knowledge, this is the first study to examine the feasibility of delivering alcohol treatment as part of routine TB care and to assess this treatment model's impact on both TB and alcohol outcomes. If proven feasible and effective, this treatment model could be adapted for patients with AUDs and co-occurring medical conditions in other settings. Specifically, this model could be used anywhere co-occurring AUDs adversely affect TB outcomes, including the United States (Brudney and Dobkin, 1991; Burman and Escarce, 1999). In addition, this strategy could integrate alcohol treatment with medical care of other chronic conditions that are affected by poor adherence due to alcohol use (Burman and Escarce, 1999; Willenbring, 2005). In particular, the greatest global challenge to treating both TB and HIV infection in populations with high rates of substance use is the successful management of substance use to ensure adherence to antiretroviral therapy (McCoy and Rodriguez, 2005; Saitz et al., 2000; Uldall et al., 2004). The successful implementation of the IMPACT study has the potential to demonstrate the importance of making appropriate adaptations to alcohol treatment strategies that are effective in one cultural and services delivery setting to a new, targeted setting where culture, language, and treatment services delivery differ from settings in which effective alcohol treatments were developed. Utilizing collaborations among an interdisciplinary, cross-cultural team is a critical process in enhancing the acceptability, feasibility, and adoption of treatment strategies in new settings where such behavioral and pharmacologic alcohol treatments are novel.

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