Protocol title:	Impact of enhancements to smartphone-based continuing care for alcohol dependence Short title: Smartphone Based Continuing Care of Alcohol
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Protocol description:	We will recruit 280 patients with moderate to severe AUD in a treatment program to test the efficacy and cost efficiency of a smartphone based application for treating alcohol addiction (ACHESS) with telephone monitoring and counseling (TMC). Participants will be randomized to: treatment as usual; ACHESS; TMC; or TMC plus ACHESS. Participation in the study lasts for 18 months with research visits at baseline, 3, 6, 9, 12, and 18 months. The intervention lasts 12 months.

Brief description

We will recruit 280 patients with moderate to severe AUD in a treatment program to test the efficacy and cost efficiency of a smartphone based application for treating alcohol addiction (ACHESS) with telephone monitoring and counseling (TMC). Participants will be randomized to: treatment as usual; ACHESS; TMC; or TMC plus ACHESS. Participation in the study lasts for 18 months with research visits at baseline, 3, 6, 9, 12, and 18 months. The intervention lasts 12 months.

Key Personnel

Study Investigator: James McKay, PhD

Study Contact: Megan Ivey

Other key personnel: Katherine Crockett, Kristin Jones, Ali Keenan, April Howard, Tyrone Thomas

Study Instruments

We will use the battery of widely used, well-validated instruments that we have used in prior studies. These include the SCID (First, et al 2002) and MINI done at baseline only. We will collect blood samples for CDT testing at both baseline and 18 months. The following will be completed at baseline, 3, 6, 9, 12, and 18 months: urine toxicology, Time-Line Follow-Back (TLFB; Sobel et al, 1996), Addiction Severity Index (ASI; Mclellan et al 1992), negative consequence of alcohol use (SIP; Miller & Tonigan, 1995, Feinn et al, 2003), abstinence-specific social support (IPA; Zywiak et al, 2009); and measures of coping (Litt et al, 2003), self-efficacy (alcohol version of the DTCQ; Annis & Martin, 1985), readiness to change (URICA; Prochaska & DiClemente, 1985), self-help involvement (McKay, et al, 1994), quality of life (SF-12; Ware et al, 1996, and EQ-5D; EuroQol Group, 1990), non-study medical services (Polsky, et al, 2010), and the modified DATCAP (French, et al, 1997).

Randomization

Urn randomization will be used to balance the groups on gender and co-occurring drug use disorder (yes/no), to ensure that the treatment conditions do not differ on these factors.

Administration of Surveys and/or Process

At baseline, the interviewer will administer the drug and alcohol sections of the SCID, MINI, Time Line Follow-Back, Addiction Severity Index, a Drug urine toxicology test, a breathalyzer, as well as instruments for Process of Change, Commitment to Abstinence, Self-Efficacy, and Self-Help. This baseline assessment will take approximately 2 hours to complete. In addition, the participant will have blood drawn to test for %cdt.

Follow up assessments will occur at 3, 6, 9, 12, and 18 months post baseline. Each follow up will include a urine drug screen, as well as completion of the ASI, Time Line Follow Back, Self-efficacy, Coping, Alcohol specific Social Support, Readiness to Change, Self-Help, and quality of life questionnaires. At the 18 month (final) research appointment, participants will again have their blood drawn. Each follow up will take approximately 1.5 hours to complete.

Data Management

All research information obtained will be kept strictly confidential. Interview and questionnaire data will be kept in locked cabinets. Subjects will be identified only by number on the computerized database. Access to identifying data will be limited to research staff engaged in the project. Our Center Data Management Unit features web-based data entry. Windows 2008 Enterprise is used to create a network structure whereby workstation and remote clients can electronically enter data through a user interface application developed in JAVA. This web interface only allows for data entry, not for querying of the full database. Databases are created in SQL Server. The restrictions are that the site requires double authentication and SSL prior to access being granted. There are no restrictions on computer location. Mr. Petro, DMU Director and primary developer of the web-based system, will be responsible for working with the project staff to ensure the integrity of the data entry process. The data will then be exported into a spreadsheet to be analyzed by the data analysts. The exported spreadsheet will not contain any PHI, as data will be coded using study identification numbers, the key list of identifiers and participant names is kept separately in a secured database with limited access and double password protected entry. Data is intended to be collected directly into this computerized system. However, due to connectivity or other computer access issues, data may need to be collected on paper and then entered into the web-based system by a research assistant. In either case, the research assistant performs the first quality assurance check for completeness and consistency (QA 1). Telephone calls that are recorded (upon consent) will require special authentication from select users to access. These recordings, therefore, will not be encrypted. Then the coordinator performs the next quality assurance review (Final QA) to maintain accuracy, completeness, and consistency. Once Final QA is complete, the record is then locked. If any further alterations need to be made, they must be done in writing through Mr. Petro.

Other sites

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Management of Information for Multi-Center Research

All participant recruitment and research will occur at and by the University of Pennsylvania. The University of Wisconsin - Madison has developed and will maintain and work with us regarding the smart phone application.

Abstract

The goal of this R01 is to determine whether adding TMC (Telephone Monitoring and Counseling) to ACHESS (Addiction version Comprehensive Health Enhancement Support System, a smart phone communication system) produces superior outcomes to those obtained with ACHESS alone. Specifically, 280 patients with moderate to severe alcohol use disorder in an intensive outpatient program (IOP) will be randomized to receive ACHESS only, TMC only, ACHESS plus TMC, or TAU (treatment as usual), in a 2 x 2 design, for 12 months. All participants will be seen for research assessments for a total of 18 months, at baseline, 3, 6, 9, 12, and 18 months post baseline. Additional analyses will examine four secondary outcome measures, including a biological measure of alcohol use, and hypothesized moderation and mediation effects. The results of the study will yield important information on improving patient alcohol use outcomes by integrating mobile automated recovery support and counselor contact.

Objectives and Hypotheses.

a. Primary Objective: To use a 2 x 2 design to test for main effects for TMC and ACHESS and the combination of TMC+ACHESS on the primary alcohol use outcome in 280 IOP participants with moderate to severe alcohol use disorder:

Hypothesis 1: Both TMC and ACHESS will generate significant main effects on % days heavy drinking across the 18-month follow-up.

Hypothesis 2: The TMC+ACHESS condition will generate lower % days heavy drinking than the TMC Only and ACHESS Only conditions across the 18-month follow-up.

b. Secondary objectives: Test three secondary hypotheses and one secondary research question:

Hypothesis 1: Treatment effects described above will also be obtained on negative consequences of drinking, a dichotomous measure of abstinence from all substances, a biological measures of alcohol use (%CDT), and on a quality of life measure.

Hypothesis 2: TMC and ACHESS effects and advantage of TMC+ACHESS over TMC Only and ACHESS Only will be greater in those with: (a) prior alcohol treatments; (b) greater alcohol use prior to IOP; and (c) alcohol use, poor social support, and low motivation in the first 3 weeks of IOP.

Hypothesis 3: Beneficial effects of ACHESS and TMC will be mediated by increases in self-efficacy, coping, social support for recovery, and readiness to change.

Compare TMC Only and ACHESS Only on primary and secondary outcomes

c. Economic objectives. Economic analyses will demonstrate that:

Hypothesis 1: TMC+ACHESS will be cost-effective relative to TMC Only and ACHESS Only

Hypothesis 2: ACHESS Only will be cost-effective relative to TMC Only

Primary outcome variable(s)*

The primary outcome measure will be percent days of heavy alcohol use (i.e., 5 drinks/day for men, 4 drinks/day for women) within each follow-up period. Studies have consistently supported the reliability and validity of the TLFB with alcohol dependent individuals. Frequency of heavy alcohol use was selected because alcohol-related problems are correlated with the frequency of heavy drinking days. This outcome is also sensitive to reductions in problematic or high-risk use, which are particularly important in a disease management model.

Secondary outcome variable(s)*

Five secondary outcomes will also be examined: alcohol use related negative consequence (SIP), any substance use within a follow-up period (yes/no, as determined by TLFB, ASI, and urine drug screens), carbohydrate deficient transferrin (%dCDT), and quality of life (as assessed with the SF-12), treatment attendance. The first two measures were selected to provide a fuller picture of overall substance use and severity of drinking consequences. Although the study interventions are primarily focused on reducing alcohol use, reductions in other drug use and negative consequences are clearly desirable and clinically important. CDT was included to provide a biological measure of heavy drinking, to corroborate results obtained with the self-report TLFB. The quality of life measure was included to obtain a more global, overall health outcome. Data will also be obtained on the frequency, timing, and total time in each ACHESS service, including when and what service each participant starts with, and where they go from there. It will also include the timing, content, and completeness of weekly and daily assessments. Finally, data will be obtained regarding treatment attendance as the number of days the participant attended treatment at the site from which we recruited them. This data will be used for economic reasons.

Background*

Role for New Communication Technology in Continuing Care.

a. Background. New Information and Communication Technologies (ICTs) may add to the efficacy of continuing care by addressing the limitations of these models, and may yield cost savings. Efficacy studies of ICTs in chronic disease self-management are promising. People with addictions tend to view ICTs favorably and they acknowledge more drug use and psychiatric symptoms online than in interviews. Further, computerized screening and brief interventions have been shown to reduce problem drinking. Interactive Voice Response, which provides prompts and collects data from people dealing with substance misuse, has been associated with reductions in alcohol use. ICTs boost motivation in health domains where social support is key to positive outcomes. A recent review found positive outcomes in 29 of 32 randomized trials of personal computer and single service (e.g. texting) cell phones for managing many different chronic diseases (e.g. addiction, pain, depression, cancer, diabetes, heart disease).

New mobile phone communication technology provides a way to bridge periods between continuing care sessions. It provides a personalized recovery support system during the evenings and on weekends when live professional counselor are unavailable. A recent review summarized findings from seven studies in which mobile phones were used to enhance psychotherapy for a range of behavioral disorders. Most of these were small pilot studies designed to determine feasibility, rather than efficacy. However, in the four studies that did calculate effects, the magnitude of effects favoring the mobile phone interventions was in the moderate-to-large range (d= .40 to 1.15). The authors concluded that more effective phone-based adjunctive interventions featured (a) better integration of the telephone technology with psychotherapy, (b) mobile telephone protocols that clearly adhered to and supported the goals of the psychotherapy, and (c) face-to-face introductions to the program. Recent studies not included in this review provide further evidence for the feasibility of using mobile phones as a component in therapy for adolescents and in borderline personality disorder. An important challenge for the alcohol treatment field is to determine how best to integrate new automated mobile recovery support technology and counselor- or therapist-delivered continuing care.

b. Work of University of Wisconsin Team on Internet Health Supports. For 25 years, Wisconsins NCI-designated Center of Excellence in Cancer Communication Research and AHRQ designated Center of Excellence in Aging Research has developed and tested ICTs to improve health behaviors, quality of life, and access to care using an evolving needs-based platform called the Comprehensive Health Enhancement Sup-port System (CHESS) for patients and family caregivers (chess.wisc.edu). In randomized efficacy trials CHESS significantly improved: (a) quality of life and self-efficacy for women with breast cancer vs. control and Internet groups, (b) quality of life and costs of care in people with HIV, (c) asthma control for young children, (d) quality of dying and survival length for lung cancer patients, and symptoms of distress in adult children of alcoholics. Clinical trials of personal computer CHESS systems are now underway for prostate cancer and families of children with bone marrow transplants.

Addiction CHESS (ACHESS) is a smart phone-based adaptation of CHESS that provides adjunctive recovery support to individuals receiving continuing care for substance use disorders. ACHESS offers easy access anytime and anywhere to 10 services tailored to meet patient needs (also see Specific Aims). Services come in text and audio-video formats, and include the following:

Social Relatedness services: one-touch links to family, others in recovery, discussion groups, and treatment staff if desired, via phone, email, and text messaging; GPS driven alerts to social supports

Coping Competence services: regular assessment of risk and protective factors to aid patient in self monitoring and inform counselors or monitors on status, tailored information on

coping, relaxation training and games to divert attention from craving, and Healthy Events Calendar.

The ACHESS system is ideally suited to address the four primary limitations in continuing care outlined earlier. Daily assessments of patients abstinence confidence, ongoing GPS monitoring, panic button functions, and weekly assessments of risks and protective factors provide clinicians and patients with access to near real-time data that are not available from weekly or bimonthly therapeutic contacts, which directly addresses heterogeneity of response and lack of between session information on patient status. The other features, including links to supporters and peers and tailored tools and information, provide more rapid access to social support and other recovery supports during periods when counselors are not immediately available. Please view a 3-min video at http://chess.wisc.edu/chess/projects/addictioncessvideo.aspx.

Although clinician to patient contact can be part of ACHESS, the majority of its functions do not require such contact. Patients choose whom they want assessment data to go to, and in many cases they select friends or family rather than counselors. When patients choose to forward information to a clinician, assessments generate alerts to clinicians only if the patient reports recent substance use, or another problem (i.e., craving) that is over a predetermined severity level. These procedures have led to relatively little contact be-tween counselors and patients in ACHESS studies (see below).

c. Alcohol Research Findings. In a completed NIAAA-funded controlled trial, alcohol dependent patients (N=349) beginning a continuing care intervention following residential treatment were randomized to receive adjunctive ACHESS for 8 months or standard continuing care only. Participants primarily were male (61%), unemployed (78%), and users of other drugs (63%); 76% had been in addiction treatment before (22% with 5+ treatments), 58% had a high school diploma or less, and 47% had co-occurring mental health diagnoses. The participants continued to use the ACHESS system at a high rate through the 8 month period over which it was provided. At the 8 month point, 70% of subjects were using ACHESS at least weekly; compared to 92% in month one. This drop off is less than any other CHESS application we have studied. Alcohol use out-comes were markedly better in the group randomized to ACHESS. Across 4, 8 and 12 month follow-ups, those who responded to all surveys (70%) reported 57% fewer heavy drinking days ($p=.003$; $d=.39$) and 30% higher rates of complete abstinence ($P=.007$; OR 1.74) in the ACHESS condition compared to TAU. Similar significance levels were found in an intent-to-treat analysis with the full sample.

Of the participants randomized to ACHESS, 28% reported a lapse or relapse at some point via ACHESS prompts in the 8 months and another 11% were designated as at risk for relapse at some point in the 8 months based on ACHESS data. In addition, most participants at some point had a score on one of the 10 assessment items that was over a predetermined threshold. Participants in this study chose whom they wanted their ACHESS data to be forwarded to: family/friends, a person who monitored ACHESS utilization, or to their counselor. When participants selected the counselor, the counselor in most cases responded to these prompts by

texting the participant, with an average of less than 2 such texts per patient per month. Slightly more than half of the participants (58%) pressed the panic button on one or more occasions, although data on how many of these incidents resulted in connection with a source of recovery support are not available.

Although one might expect that older participants would not use ACHESS as much as younger participants, in fact participants 30 years old used ACHESS slightly more than younger participants (mean of 65 vs. 59 out of 123 possible days). Moreover, only 14% of the participants in this trial reported lost or stolen phones. Results from a pilot study by Galloway et al. in which cellular telephones were given to six methamphetamine dependent outpatients for ecological momentary assessment also indicated good compliance with the protocol. Participants were called three times per day for seven weeks and they completed 65% of all possible calls, and all phones were returned at the end of the study. The findings from these studies provide strong support for the feasibility and impact of ACHESS in treatment seeking, patients with moderate to severe alcohol use disorder.

Other pilot tests of ACHESS have been conducted with participants who had alcohol use disorders. One pilot study with veterans being treated within the VA for alcohol dependence identified 30 people with 3 or more admissions to detox over an 18-month period and offered ACHESS to them. These people had 217 admissions prior and 20 subsequent to receiving ACHESS. A cost savings study is currently underway with discussions of expanding delivery of ACHESS to five other VA medical centers.

d. Limitations of ACHESS. ACHESS does not provide regular, ongoing contact with a continuing care counselor. This reduces the cost of the intervention, but could also limit its effectiveness. For example, the lack of a sustained relationship with a caregiver may reduce the positive effects that are accounted for by so-called general factors such as the therapeutic alliance. It is also not clear whether patients who have initial success and therefore limited or no contact with a counselor will use the ACHESS features to con-tact a counselor for help if they begin to struggle, or will respond to counselor outreach efforts via text messages or telephone calls. The lack of regular contact with a counselor may also lead to less utilization of ACHESS features such as monitoring and panic button messages indicating a need for help. Prior research has indicated that innovative mobile phone interventions are more effective when better integrated with psychotherapy. We hypothesize that a continuing care intervention that integrates ACHESS with regular, albeit brief, telephone contact with continuing care counselors will provide general supportive factors, facilitate more consistent and extended use of ACHESS functions, help patients plan more effectively and proactively for high risk situations, and shorten the duration and intensity of relapses should they occur.

e. Optimal ACHESS duration. It is also not clear at this point how long ACHESS needs to be provided to generate strong long-term drinking outcomes. In the recent study by Gustafson and colleagues, ACHESS was provided for 8 months to alcohol dependent patients leaving a

residential program. However, there is no strong theoretical or empirical basis for that particular duration. Therefore, we propose to test the efficacy of 6 vs. 12 months of ACHESS availability. There is evidence from reviews of continuing care studies that interventions of 12 months or more are more likely to generate positive effects than interventions of a shorter duration. Therefore, we are hypothesizing that 12 months of ACHESS will produce better outcomes than 6 months. However, the range of functions provided by ACHESS on a 24/7 basis may facilitate faster learning of new coping skills and more rapid consolidation of social support for recovery. Moreover, the combination of ACHESS with TMC for the first six months may also generate stable recovery more rapidly, thereby reducing the need for more extended recovery support and containing the cost of the intervention.

5. Telephone-Based Continuing Care. McKay and colleagues have developed a flexible, patient-centered approach to the long-term management of substance use disorders, Telephone Monitoring and Counseling (TMC). The theoretical basis of TMC comes from Stress and Coping Theory, which emphasizes the identification of high risk situations, increasing self-efficacy, and improving coping strategies; and Social Control Theory, which stresses monitoring, structure, and goal direction. These goals are also consistent with the primary goals of the Chronic Care Model, as described by Wagner et al., which include support for patient self-management, links to community resources, interventions to increase self-confidence and skill levels, a focus on goal setting, and identification of barriers to achieving goals and methods to overcome such barriers. The studies in our research program are described briefly here.

a. 12-Week Telephone Continuing Care Study. We developed an initial telephone-based intervention (TEL), which we compared to treatment as usual group counseling (GC) and relapse prevention (RP) continuing care in a randomized study with 359 IOP completers who all had current dependence on alcohol and/or cocaine. TEL produced higher abstinence rates across the 24 month follow-up than GC (p .05). Abstinence rates were somewhat higher in TEL than in RP, although not significantly so. Biological measures of heavy alcohol use (concentrations of liver enzymes) also confirmed that TEL was superior to GC and RP at 12 and 24 months. In cocaine dependent participants, there were significant group by time interactions with cocaine urine toxicology in which the advantage for TEL over GC and RP increased over the follow-up. Longitudinal mediation analyses indicated that changes in self-help involvement, self-efficacy, and commitment to abstinence accounted for the treatment effect favoring TEL over GC on abstinence outcomes.

b. Telephone-Based Adaptive Alcohol Disease Management Study. We developed an 18-month telephone-based intervention, which was compared to standard care in 252 IOP patients with current alcohol dependence who completed 3-4 weeks of IOP. Telephone Monitoring and Counseling (TMC), which was a more structured, adaptive version of the TEL intervention in the prior study, consisted of 20-30 minute telephone calls that were provided weekly for 8 weeks, twice monthly for 10 months, and monthly for the final 6 months. Each call began with a 5 minute structured assessment of risks and protective factors, followed by CBT focused on developing coping responses to the most pressing problem identified in the assessment.

During the 18 month treatment period, rates of any alcohol use (OR= 1.88) and any heavy alcohol use (OR=1.74) were significantly higher in standard care (TAU) than in TMC. Significant group x time interactions were obtained on % days alcohol and heavy alcohol use, in which the advantage for TMC over TAU increased over time. Subgroup analyses over the full 24 month follow-up showed effects favoring TMC over TAU on % days drinking were greater in women (OR=0.47, p=.04) and those with prior treatments for alcoholism (OR= 0.59, p= .02); and in those with social networks that supported continued drinking (OR=0.44, p=.02) and low readiness to change (OR=0.53, p=.05) after 3 weeks of IOP.

c. Telephone-Based Adaptive Cocaine Disease Management Study. In a similar continuing care study with cocaine dependent patients (N=321), there was significant interactions between cocaine and alcohol use at baseline and the treatment conditions (p= .03) on the primary outcome, a measure of abstinence from cocaine, other drugs, and heavy alcohol use (confirmed by urine toxicology tests). In patients with any days of cocaine or alcohol use in the 30 days prior to baseline (which included the week prior to intake and the first 3 weeks of IOP), abstinence rates were higher in TMC than in TAU, with the treatment effect larger in those who had been drinking at baseline (OR=2.47, p= .007) than in those who had been using cocaine (OR=1.95, p= .04). Conversely, in patients with no days of cocaine or alcohol use in the 30 days prior to baseline, there were no treatment effects.

d. Summary of Findings from Our Research Program. Across three major randomized controlled outcome studies, our telephone-based continuing care interventions have produced better alcohol and/or cocaine use outcomes than standard care for patients with current substance dependence (or, in the third study, substance use in the first few weeks of treatment). These projects also demonstrate our ability to collaborate successfully with publicly funded treatment programs, recruit large samples in a timely fashion, deliver novel continuing care interventions, and maintain high follow-up rates.

e. Limitations of TMC. The primary limitation of TMC is that there are periods of a week or longer between sessions when there is no contact between counselors and patients (as is the case with most behavioral interventions). The sessions help patients to process substance use episodes in the prior week, and to prepare for anticipated relapse risks in the coming week, but changes in risk factors and other live events between sessions are not monitored in near real time fashion. Therefore, the intervention has limited ability to help patients during times of crisis, or when circumstances change between sessions. In addition, TMC is not able to quickly link patients to other sources of recovery support (i.e., peers, family, community/on line resources).

Study Design: Phase II

The proposed 2x2 randomized trial employs an experimental, prospective design, in which 280 subjects with current, moderate to severe alcohol use disorder will be randomly assigned into four conditions and followed for 18 months. The follow-ups will be at 3, 6, 9, 12, and 18 months post baseline. The research assistants will be blind to the randomization to the extent possible,

though over the 18 months of participation, it is likely that the study participant will reveal their intervention.

Study duration*

In the first six months of Y1, staff from the U Penn and UWisc groups will collaborate to produce an alcohol smart phone version of ACHESS that is integrated with the TMC protocol, and counselors will be trained to use data produced by the ACHESS system as part of delivering TMC. Starting in month 7 of Y1, participants will be recruited for the clinical trial. Recruitment of participants will be completed before the end of Year 3 and follow-ups will be completed by month 52. The bulk of the data analysis and report writing will be take place during Year 5.

Resources necessary for human research protection

Sufficient office space is available at the CSA and IOPs to conduct the clinical interventions and research assessments. Laboratory facilities and personnel are available to collect and process the urine samples. Research staff will go through rigorous training and periodic retraining. The recruitment will occur at an intensive outpatient program with whom the research group has worked on many studies. The enrollment is high and in every past study the research group has reached the recruitment goal.

Target population*

The subjects will be 280 patients with current, moderate to severe alcohol use disorder, ages 18-75, who are in treatment in Philadelphia area intensive outpatient programs (IOP). Based on our previous research, we anticipate the population to look like this: The average age of this group of subjects will be about 40 years. About 75% of the subjects will be African-American, 21% will be White, and 4% will be other minorities. Approximately 10% will be Hispanic, and 40% will be female. About one-third will be employed and all will have a relatively stable residence. The population can be characterized as lower socioeconomic class.

Accrual*

Participants will be recruited from Philadelphia area IOPs. The City of Philadelphia's Department of Behavioral Health has been supportive of our research for many years and has put the PI in touch with willing IOPs. Typical Philadelphia area IOPs provide traditional, 12-step oriented treatment, delivered through 9 hours of (primarily) group counseling per week. Patients typically are retained for approximately 2 months in the program. IOP graduates are usually referred to standard outpatient care, although relatively few follow through with this.

Key inclusion criteria*

To be eligible for participation, patients must: (a) have a DSM-V diagnosis of current, moderate to severe alcohol use disorder; (b) have completed 3 weeks of IOP; (c) be 18 to 75 years of age; (d) have no current psychotic disorder or dementia severe enough to prevent participation in treatment; (e) have no acute medical problem requiring immediate inpatient treatment; (f) not be on methadone or in other forms of substance abuse treatment, other than IOP; and (g) be willing

to participate in a randomized clinical trial. Finally, subjects will (h) be able to provide the name, verified telephone number, and address of at least two contacts willing to provide locator information on the patient during follow-up, and (i) be functionally literate and have sufficient visual ability to read the smart phone. Other substance use disorders will not exclude IOP patients from participation, provided they have current alcohol moderate to severe alcohol disorder.

Key exclusion criteria*

Participants will be excluded if they (a) do not have a DSM-V diagnosis of current, moderate to severe alcohol use disorder; (b) have not completed 3 weeks of IOP; (c) are not 18 to 75 years of age; (d) have a current psychotic disorder or dementia severe enough to prevent participation in treatment; (e) have an acute medical problem requiring immediate inpatient treatment; (f) are in other forms of substance abuse treatment, other than IOP; and (g) are not willing to participate in a randomized clinical trial; (h) are not able to provide the name, verified telephone number, and address of at least two contacts willing to provide locator information on the patient during follow-up, and (i) are not functionally literate or have sufficient visual ability to read the smart phone.

Populations vulnerable to undue influence or coercion*

The population with which we work tend to be economically disadvantaged. We attempt to safe-guard them from coercion by downplaying compensation during recruitment, and by using the previously accepted pay rates of approximately $10 per hour, with a higher payment at follow-up ($50). People who have missed research visits may receive more than $50 at their next visit due to the increased information we will be asking them. Our participants are compensated for their time, and are also given $4 to compensate for their transportation to come to our offices. The rates of pay are not believed to be coercive.

Subject recruitment*

When patients enter IOP, they will be told about the study by IOP staff. Patients who express interest in participating will be referred to a study technician on site. The research technician will explain the study, obtain an initial informed consent for screening, and administer a brief instrument that collects demographic data and eligibility screening information. Patients then will be given an appointment for the baseline assessment to be conducted three weeks later. If the baseline is not scheduled at the time of screening, the research technician will schedule the appointment at a later date via telephone, or with permission from the eligible participant, via SMS text message. Patients who choose not to participate in the study will continue to receive treatment as usual. We will also display study recruitment flyers and leaflets at the recruitment sites with the site director's approval. Patients who become interested in the study from seeing our flyer or leaflet will call a study technician to complete a phone screening interview. The patient will provide verbal consent to complete the phone screen. If the patient is determined to be eligible, they will be scheduled for a baseline appointment. If the patient chooses not to participate they will continue to receive treatment as usual. At the initial baseline assessment, patients who agree to participate will sign a second informed consent, after they have

successfully passed an informed consent quiz. Patients who meet criteria for participation will then complete the remainder of the baseline assessments and be randomly assigned to one of the four treatment conditions. However, we will place eight early participants into the TMC + ACHESS treatment condition in order to ensure smooth delivery of this combined intervention prior to randomizing other participants.

Participants will be compensated $40 for completing the baseline assessments and will receive $50 for completing each follow-up assessment. Participants will be paid at the end of the research visit. Payments will be made using GreenPhire ClinCards. Clincards are reloadable prepaid cards that may be used for in-store purchases (by selecting either the "credit" or debit" option), online purchases, ATM to get cash, and cash advances at a bank. If the participant completes all assessments, their total compensation will be $290. Additionally, participants will be reimbursed $4 per visit for travel. This takes the place of SEPTA tokens that we had been providing. For those participants who we see for the 18 month follow up but have missed the preceeding follow ups, we will pay them an additional $10 for each Time Line Follow Back they provide us for the visits they missed. If they missed the 12 month research visit then the will receive $60. If they missed all the research visits between baseline and 18 months they will be paid a total of $90 ($50 for the 18 month visit, plus $10 for 3 months, $10 for 6 months, $10 for 9 months, and $10 for 12 months).

Procedures*

Baseline assessments will be conducted after the third week of IOP. The baseline visit will include consenting and gathering contact information, assessments (ASI, SCID, MINI, TLFB, and self-assessments), a urine specimen, and a blood draw. All procedures are for research purposes only and will not be part of their clinical chart at their IOP. At the completion of the baseline visit after final determination of eligibility has been completed, the participant will be randomized and will be compensated $40.00.

Participants will be randomized to either 1) ACHESS only for 12 months 2) TMC only for 12 months; 3) ACHESS with TMC for 12 months; or 4)TAU.

1. b. ACHESS Only.

Setup. During an initial face-to-face meeting with the participant, which will occur at the IOP, the counselor enters the following information into the ACHESS system: participant demographics, self-efficacy, healthy events of interest to participant, therapeutic goals and care plan, high risk locations, key relapse triggers, and attitudes toward drug use. Protocols for contact are discussed and programmed into the smart phone (i.e., high risk locations for GPS monitoring, protocols for what happens when panic button is pushed, etc.). A password will also be selected by the participant and used to protect the phone. Participants will also be trained to use the ACHESS system during this session. Follow-up training is available through brief video tutorials for each ACHESS service.

Non-emergency contacts. Participants can use the recovery support functions of ACHESS whenever they wish (see below). Following 7 days of inactivity, the system sends a message to the participant and to a member of Dr. Gustafsons staff monitoring ACHESS utilization, who will encourage ACHESS use via text messages. Technical support for ACHESS operation will be available via phone.

Assessments. Each day, ACHESS contacts participants to obtain information on confidence for maintaining abstinence. Once per week, participants are also prompted to complete a brief 10-item assessment of risk and protective factors, which is very similar to the Progress Assessment used at the start of each call in TMC. Risk factors include sleep difficulties, emotional distress, urges to drink/craving, tempting situations, and interpersonal problems. Protective factors include abstinence self-efficacy, involvement in AA or other mutual support groups, spirituality, social support, and engagement in productive activities. These items make up the Brief Addiction Monitor (BAM), which is now widely used within the VA to monitor patient progress. The areas assessed by these items have predicted relapse across many studies. ACHESS combines that information with data from prior assessments to predict relapse in the coming week. If a participant exceeds a threshold, an alert is sent to ACHESS staff and the participant is encouraged via text messages to seek additional support (see below).

Automated provision of services. ACHESS provides links to relevant resources. For participants with low abstinence confidence or worrisome scores on the risk or protective items of the progress assessment, ACHESS automatically provides suggestions of relevant coping skills. It also offers relaxation exercises, games for distraction, connections to online peer support, links to a healthy events newsletter, suggestions for diversionary activities, and contact with the participants support system.

Social support. Participants have access to discussion groups populated by other participants in the study, via online bulletin board, text messaging, or live chats. Guidelines for appropriate use of these formats are stressed while patients use ACHESS. Any mention of use of a phone for illegal purposes in ACHESS online chat rooms will result in the phone being turned off. Mobile software allows participants to text their location to pre-approved friends, family, and peers so that they can respond to requests for help.

Additional features. These include access to audio and written information on addiction, web links, GPS driven information on local self-help meetings and treatment services, inspirational messages, and reminders via texting to take medication and attend appointments. Participants may also use the smartphone to access the web and make telephone calls, so that they do not have to carry two phones.

Limitations on counselor involvement. As in Dr. Gustafsons prior ACHESS study, participants receiving ACHESS Only will not have regular contact with a continuing care counselor. Rather, when participants report low confidence or other concerning data in the weekly assessment, the system will send a message to the patient and to a member of Dr. Gustafsons staff monitoring ACHESS utilization, who will encourage more active use of

recovery supports via text messages. Participants who want to re-engage with treatment will be sent text messages urging them to contact NET and request an evaluation session.

Replacement of lost or stolen smartphones. We will provide up to one replacement smartphone to participants. For those who also lose the second phone, we will offer to load the ACHESS program onto a smartphone that they obtain on their own. The cost of replacement phones are in the budget.

2. Telephone Monitoring and Counseling Only (TMC). Participants will have one face-to-face session with the counselor who will provide TMC, to enable the counselor to develop initial rapport, explain the intervention, establish goals for the treatment, and provide a copy of a workbook to the participant. Telephone calls occur weekly for the first month, twice monthly for the next three months, monthly for months 4-7, and every other month for months 8-12 (i.e., 16 possible calls). Each call is initiated either by the counselor or the participant, depending on which method will yield the greatest likelihood of a successful connection in that case.

Each telephone call will be 15-30 minutes in duration. At the beginning of the call, the participant completes the brief Progress Assessment. These data are analyzed in real time with a computer program developed in our prior studies, which yields summary scores for risk factors, protective factors, and the ratio of risk to protective factors. Participant and counselor go over the 1-2 goals that the participant is working on, and objectives that need to be accomplished to reach each goal. Problems that were identified in the Progress Assessment are addressed, and coping behaviors for any anticipated upcoming high risk situations are identified and rehearsed. In addition, reinforcement of participant strengths and positive behaviors, and further encouragement for involvement in pro-recovery lifestyle activities are provided.

For participants randomized to this condition that do not have reliable access to a telephone, a cell phone with unlimited talk and text will be offered to allow the participant to engage in telephone counseling intervention and contact study personnel. Participants have the option to refuse the phone. At the end of the intervention, participants will be given the phone and will have to pay for phone services after that time.

3. . TMC and ACHESS (TMC+ACHESS).

General protocol. Each participant will have one face-to-face session (60-75 minutes) with the counselor who will provide the telephone intervention to him/her, to enable the counselor to develop an initial rapport with the participant, explain the protocol, and establish initial goals for the treatment. Programming of the participants smart phone, protecting it with a password, and orientation to ACHESS will also occur in this meeting. Subsequent telephone calls will occur on the same schedule as in the TMC Only condition (see above).

Obtaining and processing data on risk level. As described above, participants will be contacted daily by ACHESS and queried about their confidence in remaining abstinent for the

day and weekly to administer the brief progress assessment (noteto avoid redundancy, we will use the ACHESS BAM assessment, which is very similar to the TMC progress assessment). When participants report worrisome information in the prompts (see ACHESS description above), alerts will be sent directly to counselors as long as the participant approves. A graph with current scores and scores from the past few assessments will be sent to the counselor each week (and also forwarded to the participant, if he/she would like to receive this information). In addition, participants will be able to activate their smart phones at any time and complete additional BAM assessments if they wish to do so. These procedures will provide counselors with timely information on relapse risk.

4. Treatment as Usual (TAU). Participants in this condition will get standard care in the NET IOP, plus access to weekly step-down standard outpatient care if they complete IOP and wish to continue. They will not receive ACHESS or TMC. As is the case in virtually all public treatment programs, all treatments at NET are based on 12-step principals and are delivered almost entirely through group counseling sessions.

Regardless of the intervention and whether participants are active in the intervention, all participants will be followed for research visits at 3, 6, 9, 12, and 18 months after baseline. The schedule of assessments is described elsewhere. All assessments and procedures are for research and are not part of clinical care and will take place at our offices at 3535 Market Street, Suite 500, Philadelphia, PA.

To achieve high follow up rates, we focus on patient education and motivation, collection of extensive and verified locator information, between assessments contacts via the mail and telephone, confirmation of follow-up appointments prior to follow-up date, and standardized tracking procedures.

At the completion of each follow up, participants will be paid $50 in the form of a Greenphire ClinCard. They may receive more if they missed a preceding follow up, see compensation.

Analysis Plan*

More detailed information can be found in the grant.

Data analytic approach. The responses for the primary hypotheses comprise continuous measurements over the 3, 6, 9, 12, and 18 month follow-up points. Secondary outcomes are a mix of binary and continuous measures. Our main analyses will compare the interventions using mixed effects linear regression models for frequency (percent days) of heavy alcohol use and other continuous outcomes, and mixed effects logistic regression models for dichotomous outcomes. Given the small number of time points, we will regard time as a categorical variable,

although we may simplify the model if smoother (polynomial or spline, for example) time trends appear adequate for model fit.

Data confidentiality

How will confidentiality of data be maintained? Check all that apply

- [x] Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study.
- [x] Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords.
- [x] Prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information.
- [x] Wherever feasible, identifiers will be removed from study-related information.
- [x] A Certificate of Confidentiality will be obtained, because the research could place the subject at risk of criminal or civil liability or cause damage to the subject's financial standing, employability, or liability.
- [ ] A waiver of documentation of consent is being requested, because the only link between the subject and the study would be the consent document and the primary risk is a breach of confidentiality. (This is not an option for FDA-regulated research.)
- [x] Precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys.
- [ ] Audio and/or video recordings will be transcribed and then destroyed to eliminate audible identification of subjects.

Subject Confidentiality*

All staff have been properly trained for HIPAA awareness and human research. All staff will sign a confidentiality agreement prior to beginning work on the project, to further raise awareness of the importance of confidentiality and privacy. We will do our best to make sure that the personal information obtained during the course of this research study will be kept private. However, we cannot guarantee total privacy. If information from this study is published or presented at scientific meetings, the subject's name and other personal information will not be used. The subject will be given a subject number for the study. All the information that is provided on questionnaires and interviews will be coded with this number rather than the subject's name. Information related to the smart phone will not be related to a name - each patient will be identified by a

subject ID number. ACHESS programmers will not program identifiable information into the ACHESS program. While we can not guarantee that subjects will no program identifiable information into the phone themselves, such as contact information and meetings, we will make every attempt to review security measures with the subjects (passwords, pattern locks, refraining from using names, etc.). All study data forms will be kept in locked cabinets. The results of testing for drug or alcohol use as part of the research assessments will be provided to the subject, but will not be provided to treatment personnel in the subject's treatment program unless it is

request in writing by the subject. The questionnaires that are filled out on paper and the interviews that are completed will be kept in locked cabinets until the

information has been entered into computer files. After that, the questionnaires and forms will be kept in locked and secured storage areas at the University of Pennsylvania for 7 years. After that, they will be destroyed. The data stored in computer files will not have your name or any other identifying information attached to it. In all disclosures outside of the University of Pennsylvania Health System and School of Medicine, the subject will not be identified by name, social security number, address, telephone number, or any other direct personal identifier.

Subject Privacy*

Subjects can expect research staff to do everything possible to honor their privacy. In attempts to limit access to personal and identifiable information, potential participants will be referred to research staff by IOP staff. Prior to collecting prescreening data, a consent will be signed by the potential participant so that it is clear why they are being asked questions and what the research is about. Participants may be called on the telephone about appointments. When participants are called, researchers will identify themselves as being from the University of Pennsylvania, calling about an appointment. If the person on the other end of the line is not the potential participant, but asks about the appointment, we are not at liberty to discuss particulars and will refer the individual to the participant. Staff is instructed not to identify themselves as addictions research, or make any statements that may breech confidentiality by referring to addiction or treatment. Participants will be seen at their IOP and at our offices at 3535 Market Street. In both settings, research staff will meet with the participants in private areas and keep conversation at a low level to keep others from being able to hear what is discussed.

Data Disclosure*

The following individuals and organizations may use or disclose the subject's personal health information for this research project: The University of Pennsylvania Institutional Review Boards (the committees charged with overseeing research on human subjects) and University of Pennsylvania Office of Regulatory Affairs, The University of Pennsylvania Office of Human Research (the office which monitors research studies), and authorized members of the University of Pennsylvania and the University of Pennsylvania Health System and School of Medicine workforce who may need to access your information in the performance of their duties (for example: to provide treatment, to ensure integrity of the research, accounting or billing matters, etc.). As part of the study the Principal Investigator, study team and others listed above, may disclose the subject's personal health information, including the results of the research study tests and procedures to the following: University of Wisconsin: Dr. Gustafson and his staff will assist us in incorporating your information into the ACHESS program. This includes feedback in new text and programming. Blood samples will be tested by Dr. Ray Anton's lab at the Medical University of South Carolina. Government agency and/or their representative: National Institute on Drug Abuse, The Philadelphia Department of Public Health Institutional Review Board, and representatives of the Behavioral Health Department of the City of Philadelphia.

1. Consent Process

Overview*

Patients who express interest in participating will be referred to a study technician on site. The research technician will explain the study in a private location and allow for ample time for discussion and questions, obtain an initial informed consent for screening, and administer a brief instrument that collects demographic data and eligibility screening information. Patients then will be given an appointment for the baseline assessment to be conducted three weeks later. Patients who choose not to participate in the study will continue to receive treatment as usual. Patients who call a research technician from information provided on our recruitment forms and express interest in the study will have the study explained by the research technician, and ample time will be given for discussion and questions. The research technician will obtain verbal consent from the patient to administer a telephone screening that will collect demographic information and eligibility screening information. Eligible patients will then be scheduled for an appointment to complete the baseline assessment. Patients who choose not to participate after the telephone screening will continue to receive treatment as usual. At the initial baseline assessment three weeks later, patients who agree to participate will sign a second informed consent, after they have successfully passed an informed consent quiz. The consent document will be reviewed with the participant at research follow ups.

Potential Study Risks*

The risks of the research are conceived to be minimal (e.g., possible embarrassment) and consist of those incurred in providing self-report data on alcohol and drug-related history and problems, and social and psychiatric problems, for example embarrassment. If a potential employer were to discover you were participating in this study it may have negative consequences on your employability. As with any phone, if you lose the provided cell phone there is a risk that someone can access your contact list, therefore having not only their contact information but also be able to identify you. There is also a slight risk of bruising from the blood draws. There are minimal medical risks associated with research participation. All subjects will receive at a minimum treatment as usual in the programs from which they will be recruited.

Potential Study Benefits*

The project will yield information on the efficacy of two telephone-based continuing care models and whether the combination of a smart phone-based recovery support system and regular contact with a counselor produces better alcohol use outcomes than either intervention alone. Information will also be obtained regarding moderators and mediators of treatment effects that are obtained. This information will be of direct value to treatment providers and should help to guide future treatment efforts with this patient population.

Data and Safety Monitoring*

Dr. McKay, one of the two Principal Investigators, will be responsible for monitoring the safety and effectiveness of this trial, executing the Data and Safety Monitoring (DSM) plan, and complying with the reporting requirements. Dr. McKay will provide a summary of the DSM

report to NIAAA on an annual basis as part of the progress report. The DSM report will include the participants socio-demographic characteristics, expected versus actual recruitment rates, treatment retention rates, any quality assurance or regulatory issues that occurred during the past year, summary of SAEs, and any actions or changes with respect to the protocol. The DSM report to NIAAA will also include, when available, the results of any efficacy data analysis conducted.

Data will be collected using standardized forms and will only be identified with the studys ID of the participant. The codes that link the name of the participant and the study ID will be kept confidential by the project coordinator in a secured cabinet. Most of the study data will be entered directly into databases as it is collected, via the Penn Centers web-based data entry system. These databases are password and firewall protected, and do not contain the participants name or any other identifying information. Data forms that are not amenable to web-based data entry will be transported to the PIs data entry center, and will be entered in the computer independently by two teams of trained data entry staff, and discrepancies will be corrected by a supervisor, based on source documents. The quality of the data will be monitored once per month. The studys statistician will analyze the data, using SAS and SPSS software.

CHESS websites and mobile applications implement secure and up-to-date instances of Microsoft IIS and Microsoft SQL solutions. The hosting of CHESS IS infrastructure is comprised of a range of server class virtual machines operating on a multi-node deployment spanning throughout the University of Wisconsin Madisons engineering campus. On the client-side, users accessing secure CHESS websites and mobile application do so using pre-established log-in credentials over a 128-bit Encryption with Extended Validation (EV) HTTPS connection verified by COMODO. In order to ensure the integrity and functionality of the CHESS IS infrastructure fault tolerant methods such as layered logical and physical redundancy, environmental and access controls, as well as comprehensive backup systems are employed. Operational administration and maintenance of these systems is carried out by members of the CHESS technical team and staff from the Computer Aided Engineering Center. The policy framework with which CHESS systems adhere by include the CHESS Data and Security Monitoring Plan, the College of Engineering-Network Security Policy, and the various University of Wisconsin Madisons IT Policies.

Penn staff will have access to the use data through the A-CHESS administrative tool, a password protected site, which provides tools for an agency/provider to sign up new clients, add agency specific content as well as look at a-CHESS use data (which you can download into an excel spreadsheet). So there is really no need for UW to transmit data to Penn since you are able to access the use data on your own. If there was a need at some point for us to transmit use data we would make specific arrangements to send an encrypted file.

The primary study outcomes will be frequency of heavy drinking days (5 drinks for men, 4 drinks for women) in each period of the follow-up (e.g., months 1-3, 4-6, 7-9, 10-12, 13-18). Secondary outcome measures include alcohol related consequences, abstinence from alcohol and drugs, quality of life, and a biological measure of alcohol use (%CDT). Outcome data will be analyzed using mixed effect regressions for continuous and categorical data and various packages to examine mediation effects (i.e., MPlus). The alpha level will be set at 5%.

Data quality will be monitored by random inspection of the completed forms by the research coordinator and any problems detected will be discussed with the PI. Therapists will receive standardized training on each of the therapies, which are all manualized. Adherence to therapy techniques will be monitored using audiotapes and individual supervision provided by the clinical coordinator and the PI. If therapy drift is observed the therapists will be re-trained.

Blind interim analyses of the data will be conducted at two points when 50 and 75% of the sample has been accrued. If the results show statistically overwhelming significant differences between groups, the study will be stopped (or one of the conditions stopped).

Safety monitoring plan

During screening, study applicants will undergo a psychiatric diagnostic evaluation using a standardized interview instrument. Patients with psychiatric conditions who deteriorate significantly during the course of the study will be referred to their psychiatrists for further evaluation, and dropped from the study if warranted for safety reasons.

In this study we will use the FDA definition of serious adverse events (SAEs). SAEs will be systematically assessed at each clinic visit. Any SAE, whether or not related to study intervention, will be reported to the IRB and NIAAA. The initial SAE report will be followed by submission of a completed SAE report to both institutions. In the event that a patient either withdraws from the study or the investigator decides to discontinue a patient due to SAE, the patient will be monitored by the investigator via ongoing status assessment until either a resolution is reached (i.e., the problem requiring hospitalization has resolved or stabilized with no further changes expected), the SAE is determined to be clearly unrelated to the study intervention, or the SAE results in death. Outcome of SAEs will be periodically reported to NIAAA. A summary of the SAEs that occurred during the previous year will be included in the annual progress report to NIAAA.

Risk / Benefit Assessment* : Minimal Risk