Optimizing e-interventions for Alcohol Use: Do Common Factors Apply?

NIAAA Grant Number: R21AA023660

Principal Investigator: Emily R. Grekin, Ph.D.

NIAAA Program Official: Brett Thomas Hagman

Draft or Version Number: 1

December 5, 2018

STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the NIDCR Clinical Terms of Award. All personnel involved in the conduct of this study have completed human subject protection training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator or Clinical Site Investigator:

Signed:  Date: 5-21-19

Name: Emily R. Grekin, Ph.D.

Title: Principal Investigator

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CONSORT	Consolidated Standards of Reporting Trials
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FWA	Federalwide Assurance
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IRB	Institutional Review Board
LC-MS/MS	Liquid Chromatography-Tandem Mass Spectrometry
MOP	Manual of Procedures
N	Number (typically refers to subjects)
NIAAA	National Institute on Alcohol Abuse and Alcoholism, NIH, DHHS
NIH	National Institutes of Health
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
UP	Unanticipated Problem

PROTOCOL SUMMARY

Title:	Optimizing e-interventions for Alcohol Use: Do Common Factors Apply?
Objectives:	Primary: The primary outcome will be mean drinks per day over the past 30 days (as measured at both 1 and 3-month follow ups). Secondary: Secondary outcome measures include past month heavy drinking days, alcohol-related consequences, and intention to reduce alcohol use.
Population:	Participants will be college students age 18 and older who meet heavy drinking criteria.
Number of Sites:	Wayne State University
Description of Intervention:	This R21 clinical trial planning grant proposes the development and preliminary validation of computer-delivered brief interventions in which empathy, use of a voice and use of an animated narrator are systematically manipulated using a factorial design. We will also manipulate the presence or absence of motivational content in order to examine possible interactions between common factors and specific motivational techniques.
Study Duration:	24 months
Subject Participation Duration:	3 months (there is a 1 month and 3 month post baseline follow-up)
Estimated Time to Complete Enrollment:	21 months

Principal Investigator:
Emily R Grekin, PhD
Wayne State University
5057 Woodward Ave., 7th Floor Detroit, MI 48202
(313) 577-2820; (313) 577-7636 (fax)
grekine@wayne.edu

NIAAA Program Official:
Brett Thomas Hagman
(301) 443-0638; (301) 443-8744 (fax)
brett.hagman@nih.gov

Institutions:
Wayne State University

Other Key Personnel:
Steven Ondersma, Ph.D.
Wayne State University
Kari C Kugler, Ph.D.
Pennsylvania State University
Jennifer B. McClure, Ph.D.
University of Washington

1 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 Background Information

A. Brief Interventions for Alcohol Use

Brief interventions for alcohol use have been effective in reducing drinking (O'Donnell et al., 2013; Tanner-Smith & Lipsey, 2015; Kohler & Hofmann, 2015; Larimer & Cronce, 2007). These interventions are particularly useful for the large percentage (i.e. 87%) of problem drinkers who do not want longer-term, more intensive treatments (SAMHSA, 2012). However, the public health impact of brief interventions has been severely impeded by implementation challenges, such as limitations in time, training, and willingness among providers (e.g., Hilbink et al., 2012). Further, positive overall findings in meta-analyses obscure the results of multiple rigorous efficacy trials showing no brief intervention effect on alcohol use (e.g., Maio et al, 2005). **Both of these issues—the implementation challenges and the inconsistency in outcomes—suggest that changes are needed before brief alcohol interventions can meet their full potential.**

Technology offers exciting potential in both respects. Computer-delivered brief interventions (CDBIs) have consistently yielded small but significant effects in meta-analyses (e.g., Donoghue et al., 2014; Rooke et al., 2010; Webb et al., 2010). Further, they can be presented inexpensively, with perfect fidelity, and without the need for training or provider time. Finally—and most relevant to the present study—their replicability, flexibility, and modularity makes them an ideal platform for isolating the active ingredients that are associated with positive outcomes. Leveraging this capability could lead to optimized and increasingly effective CDBIs. Notably, however, **surprisingly little research has used this approach to identify which elements of these multi-component interventions are most strongly associated with change.** This R21 exploratory/developmental study therefore sought to identify active CDBI components, using a factorial design guided by the Multiphase Optimization Strategy (MOST; Collins et al, 2009; 2011), as well as by both Common Factors Theory (Norcross & Wampold, 2011) and Media Equation Theory (Nass & Moon 2000).

B. The Potential for Dramatic Improvement: Common Factors Theory and Media Equation Theory

Common Factors Theory suggests that therapist-delivered interventions vary in efficacy, not just as a function of their theoretical approach, but also with the characteristics of the therapist him or herself. Specifically, a set of common relationship factors (e.g., positive regard, empathy) has been clearly associated with therapy outcome (Norcross & Wampold, 2011). However, research has not examined whether attention to these factors in the context of a *computerized* intervention can similarly increase efficacy.

Media Equation Theory *(*Nass & Moon 2000) suggests that people automatically react to computers in social ways (e.g., they assign 'personalities' to computers, engage in impression management, respond to flattery, worry about 'offending' the computer, etc.). These data suggest that CDBIs have the potential to be effective, not just by providing information and/or skills training, but also by establishing a therapeutic 'relationship' with a client based on qualities such as respect and empathy.

To date, the idea of using a computer to develop a meaningful therapeutic relationship is in its infancy. It is unclear whether (1) making a CDBI more 'humanlike' (e.g., giving it a voice, adding an interactive narrator, etc.) or (2) imbuing it with facsimiles of common relationship factors (e.g. empathy, positive regard) will enhance its efficacy. The current study experimentally examined these questions by investigating whether four variables (common factors, voice, narrator, and presence of motivational content) increased the efficacy of a CDBI. In doing so, it not only fully leveraged the unique flexibility and modularity of CDBIs, allowing systematic manipulation of very specific elements; but was also the first study to systematically and experimentally examine common factors in CDBI research.

II. Research Strategy: Innovation

The current study includes a number of innovations, consistent with its status as an R21 exploratory/developmental application. Given that innovation and certainty are often partially incompatible, this exploratory research was designed to seek possible signals in an important new area, rather than to confirm effects that were already well-established. Key innovations included:

- The proposed study **was the first to experimentally evaluate the role of common factors in computer-delivered interventions**. Findings from the field of Human-Computer interaction suggest that individuals (1) react to computers in a social manner, especially when they include a voice or other "human" characteristics; Nass & Moon, 2000), and (2) respond positively to relational behaviors (e.g., flattery, empathy) expressed by computers (Bickmore et al, 2005). The current study was the first to apply these findings in a therapeutic context, or to use them to inform brief intervention development.
- The current study made use of **unique technology.** The software used in this study was highly interactive and individualized, and relied heavily on realistic interactions with a three-dimensional, animated narrator that could mimic the more conversational nature of person-delivered brief interventions. This narrator could speak, move, point, provide empathic reflections, and display emotional responses such as pleasure, surprise, sadness, and thoughtfulness. The uniquely interactive, lifelike nature of this software provides an ideal platform for examining common factors in CDBIs.
- Following the Multiphase Optimization Strategy (e.g., Collins et al., 2011), the current study used a **factorial design** to test 16 combinations of 4 common factors (Collins, Dziak, & Li, 2009). Because each participant either received or did not receive each common factor, analyses of all factors utilized the entire sample and thus were fully powered with a relatively small N. This unique factorial design allowed us to test not only the main effects of the four factors under study (one of

which is consistent with Common Factors Theory, and two of which are consistent with Media Equation Theory), but also **whether these factors interacted to result in better outcomes.**

- The current study evaluated common factors, voice, and narrator **while also systematically varying the presence vs. absence of motivational content,** by comparing it to very straightforward didactic material. This unique design element allowed us to examine the relative therapeutic contribution of specific motivational strategies, vs. simply providing information about the problem. These comparisons are particularly important given that (1) key components of brief motivational interventions (e.g., MI spirit, therapeutic alliance) have not been consistently associated with better outcomes (Bertholet et al, 2013), and (2) research-related consent, randomization, and/or assessment have been shown to have clear therapeutic effects (e.g., Ondersma et al, 2012).
- The current study was the first to examine the role of common factors using **random assignment** to conditions involving different combinations of common factors. **Virtually all existing common factors research is correlational.** As a result, it is unclear whether certain clients elicit certain reactions from therapists (e.g., motivated clients may elicit more positive, empathic responses than unmotivated clients). Additionally, it is unclear whether common factors are the cause or the result of a successful therapy outcome (i.e., does empathy cause less alcohol use or does less alcohol use elicit more empathy).

III. Research Strategy: Approach

A. Investigators and Preliminary Studies

The current application includes a team with extensive experience in all key elements of the proposed study: alcohol use among youth, CDBIs, and MOST factorial studies. The PI, Dr. Grekin, has a long-standing research program focusing on the development and maintenance of risky drinking among college students (Grekin et al, 2005, 2006, 2012; Goudriaan et al 2011). She also has experience with brief motivational interventions (particularly Dr. Ondersma's Computerized Intervention Authoring System – see below). She has conducted research examining (1) how state variables measured during a computer-delivered intervention are related to long-term substance use outcomes (Ondersma et al, 2011) and (2) how indirect screening can be used to facilitate substance use intervention without the need for self-report (Grekin et al, 2010).

Co-Investigator Ondersma has over a decade of NIH-funded experience with computer-delivered brief interventions for substance use. A member of the Motivational Interviewing Network of Trainers, his e-interventions have placed great emphasis on facsimiles of empathy, optimism, and positive regard. The efficacy of these interventions has been supported in multiple randomized trials (Ondersma et al., 2005, 2007, 2012, 2014; Naar-King et al., 2013; Schwartz et al., 2014).

Dr. Jennifer McClure's research focuses on high-reach interventions for substance use, primarily tobacco. Importantly, she is a leader with regard to use of the Multiphase Optimization Strategy (MOST) for computer-delivered interventions (e.g., see McClure et al., 2013), and, as such, will contribute important expertise and experience to the

proposed study. Dr. Kari Kugler will also contribute important expertise with MOST/factorial designs, particularly with respect to their analysis; she is a member of The Methodology Group at Penn State where MOST was developed. *Dr. George Divine is a Senior Biostatistician at Henry Ford Hospital who has worked extensively on NIH-funded health services and clinical trials research. He provided consultation on data analysis and methods of handling non-normal count data.*

This work also benefitted greatly from specialized software developed under Co-I Ondersma's previous awards. This software, called the "Computerized Intervention Authoring System," or CIAS, was designed specifically to allow easy creation and/or modification of computer-delivered content, without the need for new programming. It was also designed to be as lifelike and synchronous as possible; it includes a three-dimensional animated character capable of over 50 specific actions that can talk, read each item for the participant, act as a guide throughout the process, and provide occasional comic relief. These capabilities allow CIAS to provide empathic and emotive reflections, and allow developers to imbue the narrator with a lifelike personality. These capabilities, however, can be easily and individually turned on or off—making CIAS ideal for the study of each characteristic/capability. Previous studies using CIAS-developed interventions have yielded extremely high ratings for acceptability and ease of use (e.g., Ondersma et al., 2005, 2014).

Using the CIAS software described above, Dr. Ondersma has developed a standard brief, single session substance use intervention based on principles of motivational interviewing (Miller & Rollnick, 2002). This intervention involves three components; (a) *decisional balance, in which participants answer questions about what they like/don't like about drinking (e.g., "Right now, what would you say is the single biggest reason you drink?") (b) normed feedback, in which participants are shown graphs that illustrate where their drinking falls in relation to others their age; and (c) goal-setting, in which participants have the option of indicating a change goal, and—if setting a goal—are helped to work through a specific change plan, including a menu of change options and referral to local treatment options.*

Further, since the initial submission of this application, *Dr. Grekin has pilot tested high and low empathy versions of the intervention described above on 25 Wayne State undergraduates (all of whom met proposed study criteria; see below). Despite the small sample size, participants who were randomized to the high (versus low) empathy version scored significantly higher on 5 of 11 readiness to change items (e.g. 'How likely are you to reduce your drinking in the next week?"). No other between-group differences were found.*

1.2 Potential Risks and Benefits

1.2.1 Potential Risks

There are no known significant risks to students from participating in this study. Some students may have concerns about the confidentiality of their answers, although they

will be assured of confidentiality as stated below. In addition, professional referrals may be made if students indicate that they are actively suicidal or experiencing significant psychological distress (though this will not be specifically assessed). Minor risks may include some discomfort from answering questions about alcohol use.

1.2.2 Potential Benefits

Participants will benefit from increased understanding of psychological research. In addition, some participants may gain insight into factors which affect their alcohol use or may experience increased motivation to reduce their drinking. Upon publication, research findings will benefit society, generally, by increasing knowledge of the mechanisms underlying effective, computer-delivered interventions.

OBJECTIVES

1.3 Study Objectives/Outcome Measures

1.3.1 Primary

The primary outcome will be mean drinks per day over the past 30 days (as measured at both 1 and 3-month follow ups). Outcome data will be analyzed using ANCOVAs, factorial ordinal regression, or binary logistic regression, depending on each outcome's distribution. The alpha level will be set at 5%.

1.3.2 Secondary

Secondary outcome measures include past month heavy drinking days, alcohol-related consequences, and intention to reduce alcohol use.

3 STUDY DESIGN

The purpose of this study was to develop a maximally effective computer-delivered brief intervention (CDBI) for reducing heavy alcohol use. To accomplish this we created 16 different versions of a CDBI in which common factors, use of a voice, use of an animated narrator, and motivational content were systematically manipulated using a factorial design. Participants were 352 male and female undergraduate students at Wayne State University recruited either through the Psychology department 'subject pool' or through ads placed on the university's website. Eligible students needed to meet NIAAA--defined binge or heavy drinking criteria. Heavy drinking criteria: More than 3 (women)/4 (men) drinks per day, or more than 7 (women)/14 (men) drinks per week. Binge drinking criteria: more than 4 (women)/5 (men) drinks in a 2 hr. period.

The study consisted of a baseline assessment (45 minutes, in lab), a 1-month follow-up assessment (10 minutes, online), and a 3-month follow-up assessment (30 minutes, online). During all three assessments, participants completed questionnaires assessing demographics, past-month alcohol use, alcohol-related consequences, heavy episodic drinking, and motivation to reduce drinking. During the baseline and the 3-month follow-up assessments, participants were given a Timeline Follow-Back Interview to assess past month alcohol use. Additionally, during the baseline assessment, participants completed a brief (15 minute), computer-delivered intervention aimed at reducing heavy drinking. This intervention has been used in multiple previous studies and is based on the principles of motivational interviewing. At the end of each session, participants were fully debriefed and compensated with either course credit or an Amazon gift card ($20 gift card for the baseline session, $30 gift card for the 1-month follow-up, $40 gift card for the 3-month follow-up).

The first step in the development phase was to create, using CIAS software, 16 alternate versions of the motivational intervention described above. Alternate versions varied in the presence vs. absence of four factors (see Table 1). Two of the factors—use of a voice, and use of an animated narrator—involved "humanization" of the computer program which, according to the Media Equation Theory, will increase alliance with the software. The manipulation of common factors—operationalized as a combination of empathic reflection and expression of positive regard—allowed us to directly test the effects of common factors on CDBI outcomes. The fourth factor we manipulated was use of strategic motivational techniques, including decisional balance, normed feedback, and optional goal-setting. *Notably, experimental conditions that did not contain motivational techniques could still include common factors, as the computer can make positive/empathic statements about the participant's understanding of educational content (e.g., "I appreciate your efforts to understand this"). See Table 1, below.*

Table 1. Four factors and preliminary operationalization of present/not present distinction

	Empathy	**Human voice**	**Narrator**	**Motivational strategies**
Present	Non-judgmental reflections of responses; clear attempts to understand participant's perspective	A synthetic text to speech engine will read all content for the participant (questions will also appear on screen)	An animated narrator capable of nodding, smiling, pointing, etc.; can either talk aloud or use a speech bubble	Decisional balance, personalized normed feedback, and optional goal setting using a menu of options
Example	Drinking really helps you to relax.			
Not present	No reflections or overt attempts to elicit participant's perspective	No use of voice	No narrator	Educational content only

1. *Participants:* Participants were 352 students at Wayne State University in Detroit. *Undergraduates are an ideal population for this first stage of testing, in that (1) they are at high risk for heavy alcohol use (e.g., 40% of college students report past 2-week binge drinking; O'Malley & Johnson, 2002); (2) they have been shown to reduce alcohol use in response to CDBIs (Carey et al, 2009; Larminer et al, 2007); and (3) their accessibility allows us to efficiently and preliminarily test the proposed hypotheses of this exploratory study.*

2. *Recruitment:* Participants were recruited in 1 of 2 ways. Some of the participants were recruited from the Wayne State Psychology department subject pool, which serves between 2400 and 2500 undergraduates each year. Students in the subject pool can sign up online to participate in research being conducted in the Wayne State psychology department. Students may sign up for as many studies as they choose and participation is typically compensated with course credit. In a typical year, 10-12 studies

actively recruit from the subject pool.

Students in the subject pool were asked to complete a prescreen questionnaire before signing up for research studies. Six of the prescreen items assessed NIAAA-defined binge and heavy drinking criteria. Heavy drinking criteria: More than 3 (women)/4 (men) drinks per day, or more than 7 (women)/14 (men) drinks per week. Binge drinking criteria: more than 4 (women)/5 (men) drinks in a 2 hr. period. Subject pool students who met either binge or heavy drinking criteria were e-mailed and invited to participate in the study.

Students were also be recruited through advertisements posted on the Wayne State online portal "Pipeline." Pipeline is viewed daily by virtually all of the 17,000 undergraduates at Wayne State. Advertisements placed on Pipeline offered students who drank at least once per week the opportunity to participate in the study. Students who responded to the Pipeline advertisement were given a 3-minute phone screener to determine eligibility. *All eligible students (recruited from either the subject pool or Pipeline) were told that participation would involve completing three brief alcohol use assessments and receiving information about how their alcohol use compares to others their age.* Those who wished to participate were then signed up for a baseline session

3. Baseline Laboratory Session: Participants were met in the lab by a research assistant. After providing consent, they completed (1) a computerized Timeline Follow-Back (TLFB) interview assessing past-month drinking, and (2) computerized questionnaires that assessed demographics, mean drinks per day in the past 30 days, past month alcohol consequences, and motivation to reduce alcohol use. After completing these measures, participants were randomized to a particular version of the intervention by the computer (352 participants were assigned to 16 conditions: see Table 2, right). Each condition lasted approximately 15 minutes. Afterwards, participants completed post-intervention questionnaires assessing (1) motivation to reduce alcohol use, and (2) perceived degree of empathy and positive regard received from the intervention. At the end of the study, participants were debriefed and compensated with either course credit or a $20 Amazon gift card (participant's choice). The entire baseline session took approximately 45 minutes (10 minutes for orientation and consent, 20 min. for questionnaires/ interviews, and 15 min. for the intervention). At the end of this session, participants were given instructions about their 1 and 3-month follow-up assessments.

Table 2 Experimental Condition in 2X2X2X2 Factorial Design

Condition	Motivational Interviewing Strategies	Empathy	Animated Narrator	Voice
1	Not present	Not present	Not present	Not present
2	Not present	Not present	Not present	Present
3	Not present	Not present	Present	Not present
4	Not present	Not present	Present	Present
5	Not present	Present	Not present	Not present
6	Not present	Present	Not present	Present
7	Not present	Present	Present	Not present
8	Not present	Present	Present	Present
9	Present	Not present	Not present	Not present
10	Present	Not present	Not present	Present
11	Present	Not present	Present	Not present
12	Present	Not present	Present	Present
13	Present	Present	Not present	Not present
14	Present	Present	Not present	Present
15	Present	Present	Present	Not present
16	Present	Present	Present	Present

4. 1-Month Follow-Up Session (Online): *One month post-intervention, participants were e-mailed a link to a brief (10 minute), secure online survey (using Qualtrix) which assessed mean drinks per day in the past 30 days, past month alcohol consequences,*

and motivation to reduce alcohol use. Participants who completed the survey received either course credit or a $30 Amazon gift card (participant's choice).

5. 3-Month Follow-Up Session: *Three months post-intervention, participants were e-mailed a link to a secure (30 minute) online survey (using Qualtrix). They completed all 1-month follow-up measures, as well as a computerized TLFB interview assessing past-month drinking. At the end of the session, they were given either course credit or a $40 Amazon gift card (participant's choice).*

Measures

Past Month Alcohol Use was assessed with two measures: (1) The Timeline Follow-Back interview (Sobell & Sobell, 1966), a highly reliable interview that uses a calendar and multiple procedures to aid retrospective reporting of substance use (Fals-Stewart et al, 2000) and (2) the 3-item Quantity/Frequency questionnaire (U.S. Dept. of Health and Human Services, 1995), a survey which assesses the quantity, frequency, and maximum number of drinks consumed in the past month. Past Month Alcohol Consequences was assessed using the Brief Young Adult Alcohol Consequences Questionnaire (Read et al, 2006), a well-validated questionnaire designed to assess high and low level drinking consequences commonly experienced by young adults. Motivation to Reduce Drinking was assessed with the Readiness to Change Scale (Sobell, 1996), a 4-item scale that assesses motivation and intention to reduce drinking. Intervention Empathy and Positive Regard were assessed with the The Participant Satisfaction Questionnaire (PSQ), a measure created for this study. The PSQ assessed the degree to which participants perceived that the intervention was empathic and respectful.

3.1 Subject Inclusion/Exclusion Criteria

Inclusion criteria

Age 18 or older, currently enrolled in classes at Wayne State University, and meet NIAAA--defined binge or heavy drinking criteria. Heavy drinking criteria: More than 3 (women)/4 (men) drinks per day, or more than 7 (women)/14 (men) drinks per week. Binge drinking criteria: more than 4 (women)/5 (men) drinks in a 2 hr. period

Exclusion criteria

Frank cognitive impairment, not able to communicate in English, or not currently enrolled at Wayne State University.

3.2 Strategies for Recruitment and Retention

Many techniques and communications were employed to orient each participant from enrollment to completion of participation after follow up appointments. This includes all of the correspondences described in the Correspondence Schedule, some of which are detailed here.

3.3 Treatment Assignment Procedures

3.3.1 Randomization Procedures

Randomization was set up a priori using randomization.com to allow equal opportunity for participants to be placed in all 16 groups. All participants who screen eligible are randomized to one of sixteen conditions. In order to blind participants and research assistants 4 colors and 4 numbers were used to differentiate the 16 groups so that each group had one color and one number. The randomization list specified both the color and number to select for each participant. The PI and Project Coordinator monitor the randomization rate to ensure that equal numbers of participants are randomized to each condition.

3.3.2 Masking Procedures (if applicable)

This is a blinded study, meaning that the research assistant collecting data is blinded to the participant's randomization condition, but the PI and Project Coordinator have access to that condition. Participants are informed in the consent form that they will be randomly placed into one of the sixteen conditions. A prior randomization list of the sixteen conditions (broken down between 4 colors and 4 numbers) was generated before data collection began using the website randomization.com. The research assistant would select the appropriate color and number using the list for each participant after completing consent and before handing the participant the tablet. The correct assignment was then verified in the data when it was downloaded weekly.

3.4 Subject Withdrawal

Participants are free to withdraw from the study without changing any present or future relationship with Wayne State University or any of its affiliates. The PI may withdraw participants as well. If the PI makes this determination, participants will be told. The decision is made only to protect participants health and safety, or because the participant did not follow instructions to take part in the study.

3.4.1 Reasons for Withdrawal

Participants are notified in the consent form that their participation is voluntary and that they may withdraw from the study at any time. Participants are not obligated to provide a reason for withdrawing, though suspected reasons might include the sensitive nature of certain questions, or a lack of available time to complete assessments.

3.4.2 Handling of Subject Withdrawals or Subject Discontinuation of Study Intervention

If withdrawal occurs, this is noted on tracking spreadsheets so that the participant is no longer contacted. Subjects who unofficially withdraw due to loss to follow up are reported during progress reports.

3.5 Premature Termination or Suspension of Study

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and to the Department or Agency Head. [45 CFR 46.113; 38 CFR 16.113 Suspension or Termination of Research.]

To fulfill the regulatory requirements (as noted above), Wayne State University (WSU) has authorized the Institutional Review Board (IRB), the individual Institutional Review Boards (IRBs,Committees) and/or the Committee Chairs or the Assistant/Associate Vice President for Research (AVPR), to suspend or terminate a research project that is not being conducted in accordance with the IRB's requirements and/or that may pose increased risks and/or unacceptable risks to the safety and welfare of human research subjects. Additionally, any of the above entities or individuals can suspend the human research activities of an investigator who has committed serious or continuing non-compliance in order to assess and/or remediate the problem(s). Suspension or termination would occur when there are issues of continuing or serious noncompliance with IRB and federal requirements, when the research is associated with unexpected serious harm to research participants, or when there are immediate serious issues involving participant safety.

Key Definitions
Committee – Refers to the individual IRBs at Wayne State University.
Designee – A person appointed by the IRB Chair, acting on his/her behalf.

Confirmed Non-Compliance – Non-compliance (as defined below) that has been verified as a result of a for-cause audit or investigation.
Continuing Non-Compliance – A repeated pattern of non-compliance with all federal regulations, including Veterans regulations and guidance, by an individual investigator or research staff member either on a single protocol or multiple protocols.
Non-Compliance – The failure to comply with all federal regulations, including Veterans Administration regulations and guidance, state and local requirements, WSU Policy and determinations of the IRB.
Serious Non-Compliance – The failure to comply with all federal regulations, including Veteran's Administration regulations and guidance, state and local requirements, WSU Policy and determinations of the IRB that involve one or more of the following:

- Harm to research participants;
- Exposing research participants to a significant risk of substantive harm;
- Comprising the privacy and confidentiality of research participants;
- Damage caused to scientific integrity of the research data that has been collected;
- Willful or knowing non-compliance on the part of the investigator; and
- Adversely impacting ethical principles

(See IRB Policy: "Identifying, Defining, and Managing Non-Compliance in Human Research" for specific examples).
Suspension – A suspension occurs when the IRB Committee, IRB Chair, or AVPR places a temporary hold on the research that had been previously approved so that no new participants can be accrued, no research interventions may occur (unless necessary for the safety and well-being of the enrolled participants), and no follow-up can be conducted unless it is in the best interest of the participant and approved by the IRB.
Termination of a previously approved protocol – Termination of a previously approved protocol occurs when the IRB Committee, IRB Chair, or AVPR withdraw approval or stop all research activity permanently. No new participants may be enrolled and no additional research interventions can occur. However, future follow-up may be conducted with the approval of the IRB to monitor the well-being and any potential risk to participants.
Termination of activities that have never received prior review and approval – On the occasion when research activities have occurred that did not receive prior review and approval from the IRB, the IRB shall stop all such activities permanently. None of the data collected in this activity can be used in any future publication or presentation.
Unexpected Problem – An unexpected problem is associated with any aspect of the research study that may involve not only risks to the participant enrolled in a research study, but to other individuals who may or may not be directly associated with the research study. Unexpected problems may occur in non-clinical (behavioral or social science) as well as clinical research studies (see IRB Policy and Procedure "Unexpected Problems Involving Risk to Participants" for an inclusive list of categories).

IRB Procedures
Prior to, or during, the process of suspending or terminating a previously approved research protocol or research activities that have been conducted without prior approval, a for-cause audit will be conducted. The results of this audit will be provided to the AVPR, the IRB Chairs and Committee Members as a part of their decision to suspend and/or terminate a research protocol (see IRB Policy and Procedure "For-Cause Audit").

When other administrative groups within the University have suspended a research activity for an issue involving human participants, they are required to notify the IRB within 5 business days. An investigation will be done and an audit may be conducted by the IRB as part of their decision to suspend and/or terminate the research protocol. These results of the above actions may range from corrective or educational measures for the researcher up to and including the termination of all research activities. Further, the IRB may suspend the approval of research projects at any time during an inquiry or investigation to assure the protection of human participants.

Suspension of a Research Protocol
When reviewing an unexpected problem, the IRB or IRB designee may determine that the protocol associated with the unexpected problem should be suspended.

In addition, when there is concern that research is being conducted that is not in compliance with an approved research protocol, the IRB or IRB designee may suspend the research protocol until an internal audit has been completed. The completed audit report will be reviewed by the IRB, to determine whether or not to terminate the IRB approval.

As an alternative to termination, the IRB may impose a suspension and/or remedial actions to bring the research activities into compliance with the IRB requirements and to reduce the risk to participants. When the IRB has determined that all remedial actions have been implemented, the IRB may withdraw the suspension and the research may resume.

Termination of a Research Protocol
A research protocol is terminated:

- When a remedial action plan approved by the IRB has not been implemented; or
- When the IRB determines that it is in the best interest of the research participants.

Due to safety issues and full disclosure (as outlined in the informed consent process), participants in the research must be notified in writing of all terminations. This notification must be approved by the IRB before it is sent to participants. A plan for safe withdrawal of participants from the research is required and should consider their rights and welfare, and must be submitted to the IRB for review and approval. If follow-up of the participants for safety and effectiveness reasons is permitted or required by the IRB, the participants should be informed after obtaining IRB review and approval of the notice. Any unexpected problems or other outcomes identified during follow-up should be reported to the IRB, the research study sponsor, and the FDA, if applicable.

If the investigator wishes to resume a research protocol that has been terminated, it must be submitted as a new protocol.

Terminating Research Activities Prior to IRB Review and Approval

When research activities have occurred without prior review and approval, then all activities must cease immediately and the following process is followed:

- The PI will be required to submit an Unexpected Problem Report/Form regarding the event;
- A for-cause audit of all research documents will be conducted;
- The investigator must verify in writing that none of the data will ever be used for research purposes in the future;
- All paper documents and informed consent forms must be sent to the IRB office to be confiscated;
- All computer files must be destroyed and a signed verification submitted by the PI;
- Mandatory education of the investigator and research team will be conducted;
- Appropriate University, IRB, Agency, and Sponsor entities will be notified.

Reporting of All IRB Suspensions and/or Terminations

The suspension and/or termination of IRB approval of a research protocol will be promptly reported to the investigator by courier within 24 hours and will include a written statement of the reasons for the IRB's actions.

When research has been suspended and/or terminated, the Associate Vice President for Research will report the suspension and/or termination to other appropriate Institutional Officials, Departmental Chairs or Deans and appropriate regulatory agencies (e.g., Offices for Human Research Protection, Food and Drug Administration, Veterans Affairs, Sponsor, etc.) within 60 days of the suspension or termination (see IRB Policy and Procedure "Reporting of Unexpected Problems, Suspensions and Terminations, and Serious and Continuing Non-Compliance and the Institutional Official's Responsibilities").

For VA requirements, in addition to reporting to ORO, the following offices must be notified:

- The Privacy Office, when the report involves unauthorized use, loss, or disclosure of individually identifiable patient information.
- The Information Security Officer when the report involves violations of information security requirements.

PI Recourse

The PI may request a meeting with the AVPR, IRB Committee or IRB Chair or designee regarding any decision to suspend and/or terminate a protocol. This should be accompanied by a written appeal.

Disciplinary Action

While the IRB shall have the authority to suspend and/or terminate a research protocol, or any of an investigator's human research activities, all disciplinary action taken against an individual for being out of compliance with institutional policies regarding the protection of human participants, shall be the responsibility of the institution. The Associate/Assistant Vice President for Research shall be responsible for reporting the termination to other institutional officials (Department Chairs, Deans, the Provost, etc., as required) and to assist in taking appropriate institutional disciplinary action.

4 STUDY INTERVENTION

4.1 Study Behavioral or Social Intervention(s) Description

Sixteen versions of the intervention were created by manipulating 4 factors (voice, narrator, common factors and MI content) in a full factorial design. In conditions with a voice, all content was read aloud to participants through headphones; in non-voice conditions, content was presented exclusively as text on screen.

In conditions with a narrator, participants interacted with an animated, three-dimensional parrot who is capable of multiple specific actions (e.g., pointing, waving, yawning, etc.). The animated parrot was selected for his high likeability ratings in previous research (Ondersma, Chase, Svikis, Schuster, 2005) and the fact that (as a non-human character) he has no race or ethnicity.

In high empathy conditions, participants were exposed to a series of non-judgmental reflections and statements of affirmation that were tailored to their individual responses (e.g., “You’ve felt really stuck” or “It sounds like you feel two ways about this”). In low empathy conditions, these reflections/affirmations were absent, but all other content was identical. We chose to focus on empathy, rather than other relationship factors, because the provision of empathy has consistently been associated with better therapy outcomes in meta-analyses (e.g. Elliot et al, 2011), and because it was relatively easy to operationalize with our software.

In motivational strategy conditions, participants were presented with three specific strategies: (1) personalized normed feedback showing how the participant’s drinking compared to that of same-age peers; (2) decisional balance (i.e. weighing the pros and cons of drinking); and (3) an optional goal-setting component in which participants were given the choice to set a drinking reduction goal. Non-motivational strategy conditions provided straightforward, non-tailored didactic information about alcohol use.

Research Design

As noted above, the current study used a 2X2X2X2 factorial design to test 16 combinations of the 4 CDBI factors described above (Collins et al, 2016). Factorial designs differ from 2-arm, randomized controlled trials (RCTs) in several ways. First, factorial designs randomly assign the entire sample to all levels of *each* independent variable. This allows each main effect to be powered based on the entire sample rather than a fraction of the sample (as with RCTs). This efficiency makes factorial designs ideal for optimization. Further, when it comes time for analysis, use of effect coding (-1, 1) rather than dummy coding (0, 1) renders orthogonal all main and interaction effects, thereby increasing power for detection of interaction effects (Collins et al, 2016).

4.2 Administration of Intervention

The computerized intervention is delivered by a tablet with the aid of CIAS. This eliminates fidelity concerns because, pending no software glitches, packages are delivered the same way every time. At baseline lab visit after consent is complete, the RA sets up the participant on the tablet (selecting both the color and number listed next on the randomization list). Participants then use the tablet to complete both the assessment questions and the intervention. Pictures and intervention slides appear on-screen, as well as questions and response options. Feedback regarding satisfaction and change beliefs is collected by the tablet post-intervention. All data collected during tablet administration is transferred to the Wayne State server via an encrypted and protected transmission system.

4.3 Procedures for Training Interventionists and Monitoring Intervention Fidelity

The intervention as described above does not require training interventionists or monitoring intervention fidelity in the traditional sense. Rather, the CIAS-authored intervention is delivered via the internet to the tablet computer for participants to interact and answer questions. CIAS is routinely checked for issues, though none have been found to date that were not easily fixed. Data is also analyzed for out-of-range values or entry errors monthly so that they may be identified, logged, and prevented in the future. This ensures an extremely high level of intervention fidelity and trial administration in general.

5 STUDY SCHEDULE

- Day 1
  - Recruit into study
  - Confirm contact information
  - Emphasize follow-up and explain how links to surveys and payments will be emailed

- 1-month follow-up (emailed 1-5 times from 2 weeks before due date to 2 weeks after due date)
  - An email is sent with the survey link and a reminder of their participant ID.
  - Several emails are sent within the time frame (if necessary) to remind the participant
  - Once participant completes the following email is sent:

Hello ,
Below you will find the claim code for your $30 Amazon Gift card. This is for the compensation for completing session 2 of the College Alcohol Study. Thank you for your patience.
Gift Card Number:
Claim Code:
Thank you for your participation!
Best,
Grekin Lab

- 3-month follow-up (emailed 1-5 times from 2 weeks before due date to 2 weeks after due date)
  - An email is sent with the survey link and a reminder of their participant ID.
  - Several emails are sent (if necessary) within the time frame to remind the participant
  - Once participant completes the following email is sent:

Hello ,
Below you will find the claim code for your $40 Amazon Gift card. This is for the compensation for completing session 3 of the College Alcohol Study. Thank you for your patience.
Gift Card Number:
Claim Code:
Thank you for your participation!
Best,
Grekin Lab

- At study completion
  - Participants are emailed a debriefing letter for the study and final gift card information

5.1 Screening and Recruitment

Participants were 352 male and female undergraduate students at Wayne State University in Detroit (50.9% male; 50.9% Caucasian).

Participants were recruited in 1 of 2 ways. Some participants were recruited from the Wayne State Psychology department subject pool, which serves between 2400 and 2500 undergraduates each year. These students were asked to complete a prescreen questionnaire which assessed NIAAA-defined binge and heavy drinking criteria. Heavy drinking criteria: More than 3 (women)/4 (men) drinks per day, or more than 7 (women)/14 (men) drinks per week. Binge drinking criteria: more than 4 (women)/5 (men) drinks in a 2 hr. period. Subject pool students who met either binge or heavy drinking criteria were e-mailed and invited to participate in the study.

A second group of students was recruited through advertisements posted on the Wayne State online portal “Pipeline.” Advertisements placed on Pipeline offered students who drank at least once per week the opportunity to participate in a study on “Undergraduate Alcohol Use.” Students who responded to the Pipeline advertisement were given a 3-minute phone screener to determine eligibility.

All eligible students (recruited from either the subject pool or Pipeline) were told that participation involved completing three brief alcohol use assessments and receiving information about how their alcohol use compares to others their age. Those who wished to participate were then signed up for a baseline session.

5.2 Enrollment/Baseline

Participants meeting all eligibility criteria were given the opportunity to set up a baseline session. Upon arriving in the laboratory, participants completed a written consent form. The PI’s research assistants reviewed the consent form with participants and were available to answer any questions related to consent. A copy of the signed consent form was provided to participants. Names and phone numbers of both the PI and the Wayne State Institutional Review Board were provided in these consent forms. The original consent forms were kept in a locked file cabinet in the PI’s office, separate from all other data.

Brief Alcohol e-Intervention Study (MOST)

Time started:_____ Time end:_____

_____ Read Consent form with participant and had them provide signature.

- Answered all questions? Yes No
- Agreed to participate? Yes No
- Participant signed consent? Yes No

(Retain signed consent for records)

_____ Checked Randomization Sheet and selected color and number for package (Green/Orange use one tablet-WITH SOUND; Yellow/Purple use another tablet-NO SOUND)

*To turn off sound. Push down on Peedy. Select "Advanced Character Options." Check "Display spoken output in word bubbles," and uncheck "Play spoken audio."

_____ Begin CIAS intervention for participant and obtained CIAS ID (exit CIAS after you get the ID)

CIAS ID# _____

_____ Completed TLFB with participant in Qualtrics
**PUT CIAS ID IN QUALTRICS

_____ Reopen CIAS and begin intervention (enter the CIAS ID)

*Always put first name in (for Green/Orange, may need to write phonetically; for Yellow/Purple, always write as spelled with capital letter at beginning)

* Will need to hit "Next" on blank screen with "Screening" title

_____ Discussed follow-up and scheduled 3 month lab visit

Date scheduled: _____

_____ Marked the Google calendar for session 2 and session 3 using CIAS ID #

_____ Gave SONA credits or Gift card (please circle)
Gift card # _____

_____ Gave participant a copy of the consent form, flyer, and resource sheet
The resource sheet is only given to participants at the 3rd session

_____ E-mailed initials, CIAS ID#s, and contact info to the grekinlab email, gift card number

_____ Update CIAS ID on the Google calendar

5.3 Follow-ups (1-month and 3-month)

This study was designed to maximize the follow-up rate and therefore both follow-ups were administered online. One month post-intervention, participants were e-mailed a link to a brief (10 minute), secure online survey (using Qualtrics) which assessed mean drinks per day in the past 30 days, past month alcohol consequences, and motivation to reduce alcohol use. Participants who completed the survey received either course credit or a $30 gift card (participant's choice).

The 3-Month Follow-Up online survey (using Qualtrics) included all 1-month follow-up measures, as well as a computerized TLFB interview assessing past-month drinking. At the end of the session, Participants were given either course credit or a $40 gift card (participant's choice).

The gift cards were sent to participants' email address after the project coordinator confirmed completion of the online survey. At the very end of the study, all participants were emailed a debriefing letter describing the study in more detail.

An Explanation of the College Alcohol Study

Thank you for participating in the College Alcohol Study. We really appreciate your time and effort. Since you've just completed your last session, we want to explain to you what our study is about.

As you know, drinking alcohol can be associated with both good things, like relaxation, and bad things, like health problems. As a result, many people have mixed feelings about whether they want to reduce their alcohol use.

A number of different programs have been developed to help people better understand the pros and cons of drinking and decide whether it's worth it to them to reduce their alcohol use. However, these programs can be very different from one another. Some programs are computerized (like the one you interacted with during your first visit), whereas others use an actual person. Programs can also differ in their content and presentation. Currently, it's not clear which types of programs are most effective in helping people decide whether or not they want to change their drinking patterns.

Participants in this study are exposed to 1 of 16 different versions of a computer program. These versions differ in a number of ways. For example, some contain a voice, or animated narrator, whereas, others ask participants to read text on the computer screen. Some versions contain a large number of empathic statements, whereas others are more neutral. The goal of the current study is to examine which of these 16 versions has the greatest effect on people's decision to reduce - or not to reduce - their alcohol use 1 and 3 months later.

We realize that many people are not interested in reducing their alcohol use. We also realize that some people want to reduce their alcohol use, but not right now. We've tried to design computer programs that take those facts into consideration and help participants clarify their own, individual goals.

Again, we want to thank you for being in our study. Your participation will help us learn more about alcohol use among college students. If you have any questions, please feel free to contact use at *grekinlab@wayne.edu* or 313-577-9305.

Emily Grekin, Ph.D.
Associate Professor, Psychology
Principal Investigator, College Alcohol Study

6 ASSESSMENT OF SAFETY

During recruitment it is explained to the participant that this is a research study. They are also told the types of questions that will be asked and that they have the right to decline participation or withdrawal at any time. Participants are also explained the potential risk of distress due to the sensitive nature of the questions. The participant is explained their rights and what the study is clearly.

6.1 Specification of Safety Parameters

6.1.1 Unanticipated Problems

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

6.1.2 Adverse Events

An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

6.1.3 Serious Adverse Events

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of existing hospitalization

- Results in a persistent or significant disability or incapacity

6.2 Characteristics of an Adverse Event

6.2.1 Relationship to Study Intervention

To assess relationship of an event to study intervention, the following guidelines are used:

1. Related (Possible, Probable, Definite)
    a. The event is known to occur with the study intervention.
    b. There is a temporal relationship between the intervention and event onset.
    c. The event abates when the intervention is discontinued.
2. Not Related (Unlikely, Not Related)
    a. There is no temporal relationship between the intervention and event onset.
    b. An alternate etiology has been established.

6.2.2 Expectedness of SAEs

The Study PI will be responsible for determining whether an SAE is expected or unexpected. An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention.

6.2.3 Severity of Event

The following scale will be used to grade adverse events:

1. Mild: no intervention required; no impact on activities of daily living (ADL)
2. Moderate: minimal, local, or non-invasive intervention indicated; moderate impact on ADL
3. Severe: significant symptoms requiring invasive intervention; subject seeks medical attention, needs major assistance with ADL

6.3 Reporting Procedures

6.3.1 Unanticipated Problem Reporting to IRB and NIAAA

Incidents or events that meet the OHRP criteria for unanticipated problems require the creation and completion of an unanticipated problem report form. OHRP recommends that investigators include the following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB:

- appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number;
- a detailed description of the adverse event, incident, experience, or outcome;
- an explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem;
- a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

- Unanticipated problems that are serious adverse events will be reported to the IRB and to NIAAA within 1 week of the investigator becoming aware of the event.
- Any other unanticipated problem will be reported to the IRB and to NIAAA within 2 weeks of the investigator becoming aware of the problem.
- All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the investigator.

6.3.2 Serious Adverse Event Reporting to NIAAA

Procedures and timeline for reporting AEs to NIAAA.

AEs will be reported to the NIAAA PO at least once per year as a part of the annual progress report. These reports will describe the event, when it occurred, the study arm of the participant, and the outcome/resolution. If there are no AEs in a given year, the report will include a statement to this effect.

Procedures and timeline for reporting SAEs to NIAAA.

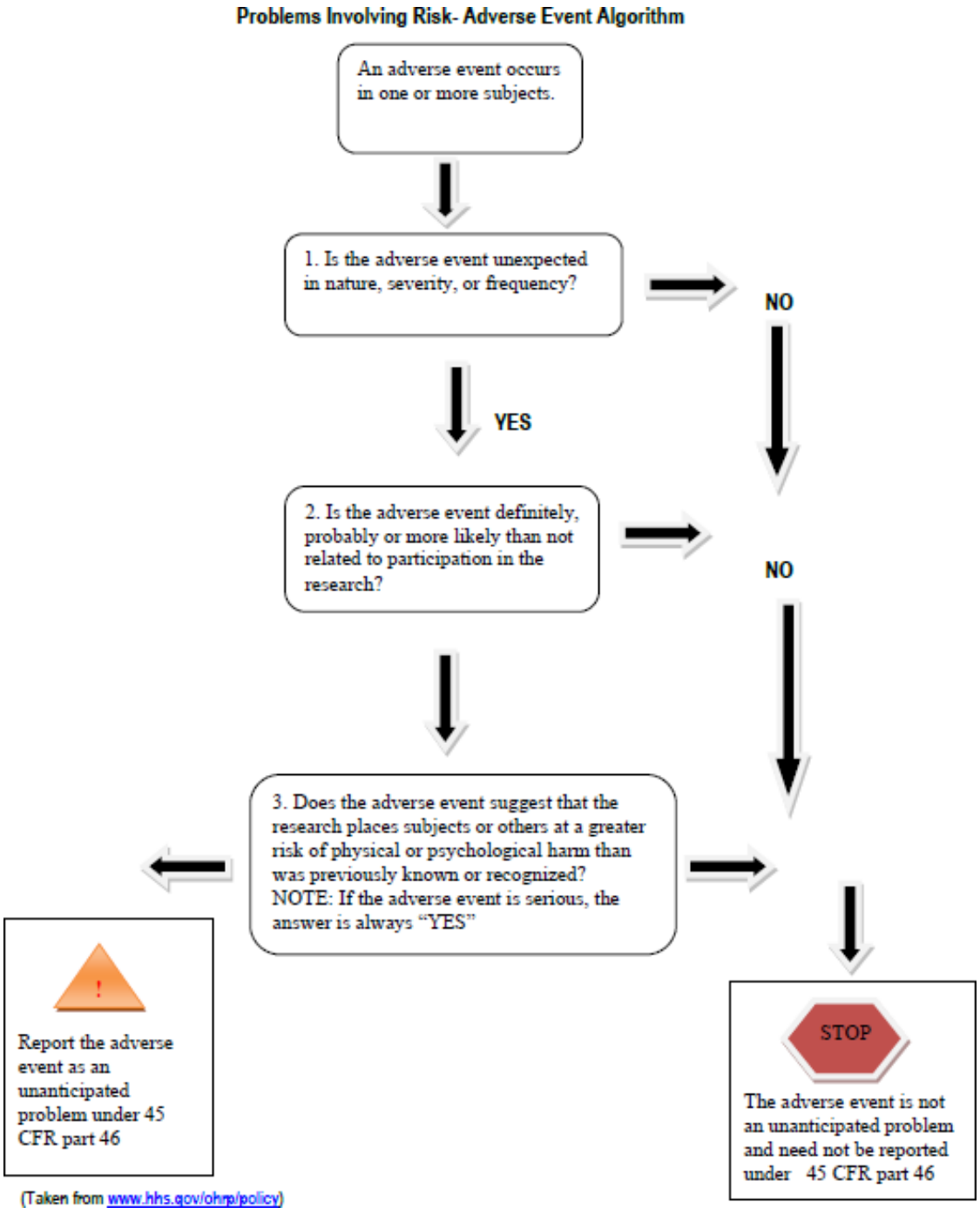
SAEs, whether or not anticipated, will be reported to the NIAAA PO within 24 hours of the event by email. This 24 hour notification will include a brief explanation of the SAE

and when it occurred. A written follow up will be sent within 72 hours of the event. This written follow up will include information on the date of the event, what occurred, actions taken by project staff, planned follow up (if any), the intervention group/study arm of the affected participant, whether the event appears to be related to the intervention, and whether participant will continue in the study.

Reporting of IRB actions to NIAAA.

Follow-up reports to the NIAAA program official—made within 48 hours of IRB actions—will specify IRB actions related to study shut-down or changes. We will follow Wayne State University policy in the handling of all AEs and SAEs; see Appendix 1 for algorithm from the WSU IRB, which will be followed in all respects except with regard to unanticipated SAEs, which **will** be reported to NIAAA.

Wayne State University Risk-Adverse Event Algorithm:



(Taken from www.hhs.gov/ohrp/policy)

7 STUDY OVERSIGHT

The Principal Investigator was responsible for monitoring the safety and efficacy of the interventions, executing the Data and Safety Monitoring Plan (DSM), and complying with all reporting requirements. The PI will provide a DSM report to NIAAA on an annual basis, as part of the progress report. The DSM report will include the participants' sociodemographic characteristics, expected versus actual recruitment rates, treatment retention rates, any quality assurance or regulatory issues that occurred during the past year, summary of adverse events (AEs) and serious adverse events (SAEs), and any actions or changes with respect to the protocol. The report will also include, when available, the results of any efficacy data analysis conducted.

a. Data Monitoring Plan. Data was collected by researcher entry (interviews) or by direct participant entry (self-report) using secure technology (CIAS and Qualtrics; both of which use strong encryption and other data safety protocols). The codes that link participant names with study ID# were secured by the PI in a locked cabinet. All data was kept in the PI's lab.

The primary outcome was mean drinks per day over the past 30 days (as measured at both 1 and 3-month follow ups). Secondary outcome measures included past month heavy drinking days, alcohol-related consequences, and intention to reduce alcohol use. Outcome data was analyzed using ANCOVAs, factorial ordinal regression, or binary logistic regression, depending on each outcome's distribution. The alpha level will be set at 5%.

Data quality was facilitated by direct participant entry of most data directly into sophisticated data collection software, and use of double-entry for all data not entered directly by participants. Data quality was monitored regularly by Co-Investigator Beatty (at Wayne State), in concert with the PI and Co-Investigator.

b. Safety Monitoring Plan. For this study, we used the FDA definition of serious adverse events (SAEs). 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 participant either withdraws from the study or the investigator decides to discontinue a participant due to a SAE, the participant will be monitored by the investigator via ongoing status assessment until (1) a resolution is reached (i.e., the problem requiring hospitalization has resolved or stabilized with no further changes expected); (2) the SAE is determined to be clearly unrelated to the study intervention; or (3) the SAE results in death. Outcomes 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.

8 STATISTICAL CONSIDERATIONS

8.1 Study Hypotheses

Factorial designs differ from randomized trials in several ways. Perhaps most importantly, in factorial designs each participant either receives or does not receive **each** independent variable. This allows analysis of each factor to utilize the entire sample, which in turn allows each main effect to be powered based on the entire sample rather than a fraction of the sample (as with randomized clinical trials). This efficiency makes factorial designs ideal for pre-trial optimization. Further, use of effect coding (-1, 1) rather than dummy coding (0, 1) renders orthogonal all main and interaction effects, increasing power for detection of interaction effects (Collins, 2009). Although R21 studies are not typically fully powered, the current N of 352, presuming use of intent to treat analysis, provides 80% power to detect main/interaction effects of d ≥ .3.

Analyses will follow standard procedures for evaluating distributional assumptions, disproportionate or biased follow-up, and randomization success, and will utilize transformations and replacement of missing data using multiple imputation as appropriate. Primary analyses will evaluate main and interaction effects on mean drinks/day in the past 30 days, as measured by both the TLFB and the Quantity/Frequency Questionnaire. (Secondary analyses will similarly examine main and interaction effects on binge drinking days, drinking consequences, and pre-post changes in intention to reduce drinking.) A single 2X2X2X2X2 ANCOVA *(or factorial ordinal/binary logistic regression, depending outcome distribution)* will test the following hypotheses:

- **Hypothesis 1.** There will be significant main effects on mean drinks/day for the two factors consistent with Common Factors Theory (empathy and positive regard).
- **Hypothesis 2.** There will be significant main effects on mean drinks/day for the two factors consistent with the Media Equation Theory (voice and narrator).
- **Hypothesis 3.** *There will be significant main effects on mean drinks/day for motivational content.*
- **Hypothesis 4.** Mean drinks/day will be lower when one or more of the common factors (empathy, positive regard) is combined with a voice and/or a narrator.
- **Hypothesis 5.** *Mean drinks/day will be lower when motivational content is combined with one or more common factors and/or with voice/narrator.*

Following MOST guidelines (Collins et al, 2009), if intervention components (or combinations of components) are clearly effective, we will proceed to developing an optimized intervention. If intervention components show some effectiveness, we will conduct refining experiments to explore what form/dose of the components will maximize effects. If there are no significant main or interaction effects, we will conduct additional exploratory/developmental studies using new factors.

V. Research Strategy: Limitations and Design Considerations

Given its status as an R21 application, this research aims to be innovative and to seek evidence of preliminary effects in an important area of research. Additionally, we note the following design considerations.

1. **Should we use college student participants?** *CDBIs for undergraduates generally contain the same content as those administered to clinical and community samples (e.g., normed feedback, change plan, etc; Larimer et al, 2007). Moreover, effect sizes for CDBIs in college vs. non-college samples do not differ (Portnoy et al, 2008). This initial, exploratory study will allow us to recruit participants in high numbers and over a short time period. We will test for generalizability—which we expect to be present—in future studies.*
2. **Are we under-powered?** Our proposed sample (N=352) will give us marginally sufficient power (80% power to detect effects up to d=.3). However, R21 exploratory studies typically lack even marginally sufficient power; we see this as a large exploratory study rather than as an underpowered confirmatory study, with its size made possible by our intentional use of a readily available sample.

9 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Study staff will maintain appropriate medical and research records for this study, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Study staff will permit authorized representatives of NIAAA and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

10 QUALITY CONTROL AND QUALITY ASSURANCE

The accuracy with which data input matches data output using the software was exhaustively checked prior to beginning the trial (using sample protocols).We have never found data coding errors on the part of the software in all previous trials. Although no problems are expected given past experiences with this technology, any evidence of errors in data recording by the ACASI will result in dropping all participants since the last quality check. Data will be checked once per month for out of range values and other quality issues. Data from participants will be accessible only with appropriate passwords known only to the PI and project coordinator.

The PI, the project manager, and the RA will meet regularly and review all data collection procedures, as well as recent data, to ensure that study procedures are being followed appropriately and all data are present.

11 ETHICS/PROTECTION OF HUMAN SUBJECTS

11.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

11.2 Institutional Review Board

The Wayne State University Internal Review Board (IRB) oversees research to ensure the safe and ethical conduct of human participant research by all faculty, staff, and students of WSU. This includes reviews of proposed research, oversight committees, continuing oversight for compliance with regulations and policy, quality assurance, and education and training for investigators, staff, and committee members. The IRB is initially notified of proposed research prior to securement of funding and works with investigators to optimize study design, data collection, and associated consents and information sheets. After approval of study protocols, any changes must be submitted to the IRB via amendments. A yearly continuation is necessary so long as research is active; at this time, staff update the IRB of currently approved forms, enrollment figures, participant demographics, preliminary results (if applicable), and other pertinent information that allows the Board to determine study execution success and participant safety and protections. Upon discovering any adverse events, the Coordinator and PI are required to file a report with the IRB and perform any suggested response actions. Finally, the IRB assists staff in closing the study once data collection has been finalized.

11.3 Informed Consent Process

We will utilize written informed consent for those who meet all inclusion and exclusion criteria. This consent form will be summarized by the research assistant and also read, if the participant wishes. The consent form will describe the nature of the possible interventions, the kinds of questions that will be asked, follow-up procedures, the participant's right to decline or quit at any time, and the possibility of distress as a result of some of the questions or material. Participants will also be told that their data will be identified by a code number only, with the only link between that code and their data being a single form kept locked in the PI's office. Finally, although we will not ask any questions that might elicit reportable information in these areas, the consent form will clearly note the possible need to breach confidentiality should the investigators become aware of reportable information regarding child abuse, neglect, suicide risk, or infectious disease.

11.4 Inclusion of Women and Minorities (Special Populations)

Participants will be 352 male and female undergraduate students at Wayne State University in Detroit. The majority of participants will be recruited from the Wayne State Psychology department subject pool which serves between 2400 and 2500 undergraduates each year. Currently, the subject pool is 72% female, 40% Caucasian, 19% African-American, 18% Arab, 13% Asian, 4% Multiracial, 3% Hispanic, and 3% 'Other.' A subset of participants will also be recruited through advertisements posted on the Wayne State University webpage. The undergraduate population, as a whole, at Wayne State is 55% female, 53% Caucasian, 21% African-American, 8% Asian, 8% 'Unknown' race/ethnicity, 5% Hispanic, 3% Multiracial, and 2% 'Other.'

11.5 Subject Confidentiality

Subject confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and any study information relating to subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor. The authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study subjects. The clinical study site will permit access to such records.

Breaches of confidentiality will be prevented in a number of ways. First, we will strictly separate identifying information and data, connecting them only via a linking table (with a hard copy kept in a locked file cabinet in the PI's lab, and a password-protected electronic version kept on a secure WSU server). Old versions of the paper linking table will be shredded; the table will only be accessible by the PI and Project Coordinator. Second, breaches will also be prevented by encrypting all ACASI data in transit using AES-256 encryption (the highest level possible). Third, breaches will be prevented by further protecting saved data with extremely strong passphrases (combining capital letters, lowercase letters, and numbers, using at least 12 characters, and changing them monthly). Fourth, all study computers will be protected with a very strong passphrase.

Should a breach be discovered, it will be reported within 24 hours to the WSU IRB and to NIAAA officials, followed by a written report within 72 hours. In addition to addressing and correcting the source of the breach, discussions with the IRB, the study DSMB, and NIAAA will determine whether study participants must be notified of the breach.

12 DATA HANDLING AND RECORD KEEPING

12.1 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. Unanticipated problems and adverse events must be reviewed by the investigator or designee.

12.2 Data Capture Methods

Most data will be collected using computer-based self-interview (ACASI) technology on a Tablet computer, with data being encrypted in transit and stored on a secure server; further, all data in the ACASI system will only be identified only with a non-identifying ID number for the participant. A single paper copy of the table linking this number to the participant's name will be kept locked in a file cabinet in the PI's lab, with a password protected electronic version stored on a secure WSU server with restricted access, such that only the PI and the Project Coordinator will have access to the server and to the passwords for the linking table file. The PI's lab is kept locked, in a locked and alarmed secure building on campus.

12.3 Data Entry

Data entry for all self-report measures will be completed directly by the participant onto a tablet computer using the ACASI software.

Regarding the ACASI: the accuracy with which data input matches data output will be exhaustively checked prior to beginning the trial, using sample protocols. (Note: we have never found data coding errors on the part of the software in all previous trials.) Further, we will test a randomly chosen sample protocol monthly following trial initiation. Although no problems are expected given past experiences with this technology, any evidence of errors in data recording by the ACASI will result in dropping all participants since the last quality check. In addition, data will be checked once per month for out of range values and other quality issues. All data will be accessible only with appropriate passwords known only to the PI and project coordinator.

12.4 Schedule and Content of Reports

PI, the project manager, and the RA will meet at least monthly while data collection is ongoing, to review all data collection procedures, as well as recent data, to ensure that study procedures are being followed appropriately and all data are present.

12.5 Study Records Retention

Study records will be maintained for at least three years from the date that the grant federal financial report (FFR) is submitted to the NIH.

12.6 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol, Good Clinical Practice, or Manual of Procedures requirements. The noncompliance may be on the part of the subject, the investigator, or study staff. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly.

These practices are consistent with investigator and sponsor obligations in ICH E6:

- Compliance with Protocol, Sections 4.5.1, 4.5.2, 4.5.3, and 4.5.4.
- Quality Assurance and Quality Control, Section 5.1.1
- Noncompliance, Sections 5.20.1 and 5.20.2.

All deviations from the protocol must be addressed in study subject source documents and promptly reported to NIAAA and the local IRB, according to their requirements.

13 PUBLICATION/DATA SHARING POLICY

This study will comply with the *NIH Public Access Policy*, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study also follows the policy that requires that all clinical trials be registered in a public trials registry such as *ClinicalTrials.gov*, which is sponsored by the National Library of Medicine. The Clinical Trials registration number for this study is **NCT02952872**.

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