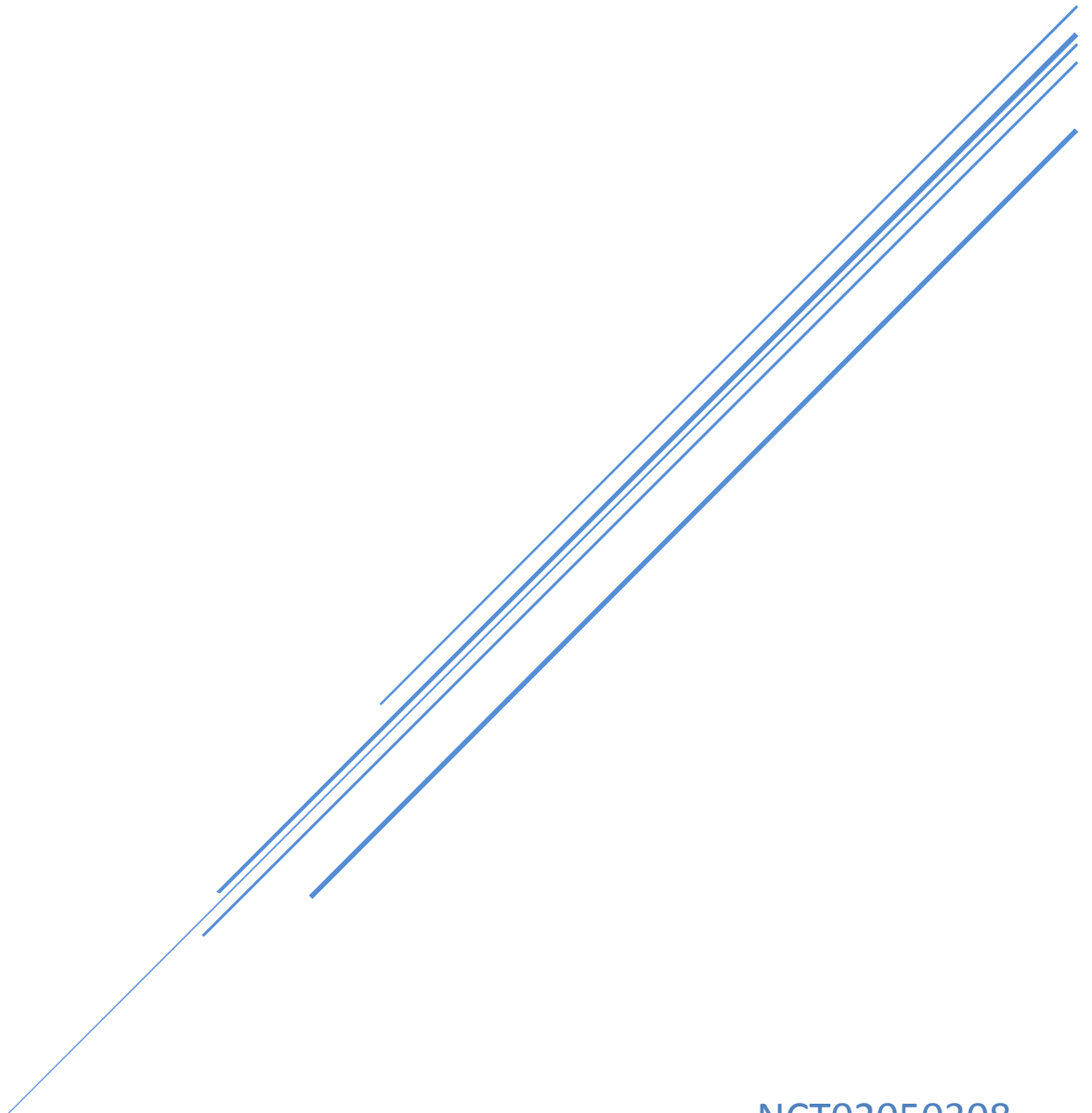


WEB-BASED SMOKING CESSATION PROGRAM FOR TRIBAL COLLEGE STUDENTS

Study Protocol



NCT02050308
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I. Rationale and Specific Aims

Many of the approximately 25,000 American Indian (AI) students enrolled in tribal colleges/universities in the US arrive there as smokers. A 2011 study of high school seniors reported that the smoking prevalence among AI students is approximately 40%, the highest rate among all racial and ethnic groups studied. Although prevalence data on smoking among AI college students are limited, studies have shown that the majority of smokers in high school continue to smoke once they reach college. Prohibited from marketing to adolescents and children, the tobacco industry in recent years has shifted its most intense marketing to college students, resulting in increases in smoking rates among them. The transition to college provides ample opportunities for young adults to acquire new and harmful habits. Many of these habits do not seem so alien to young AIs: Cigarette smoking is the number one cause of preventable death among AIs. Cancer is the second leading cause of death among AIs, and lung cancer is the leading cause of cancer deaths for both AI men and women. Cultural factors, socioeconomic circumstances, and lack of culturally-tailored cessation programs for American Indian tribal college students have prevented access to effective interventions that promote smoking cessation. To date, few studies have focused on methods to encourage smoking cessation among tribal college students and no randomized clinical trials have yet been conducted. To address this public health deficit, we propose an innovative, effective, culturally and individually-tailored smoking cessation programs to promote cessation.

Over the past 8 years, we developed a culturally-tailored, in-person, group-based adult smoking cessation program (All Nations Breath of Life – ANBL) using community-based participatory research methods. It takes into account the sacred role of tobacco among many American Indians and how culture affects smoking cessation among AIs. Preliminary data from our recent studies indicate that the internet may be more favorable and appropriate method for reaching younger and more mobile tribal college populations. Web interactivity, immediacy of feedback, and wider reach and accessibility will, we believe, contribute to greater success of the intervention. This proposal is an extension of our previous work. In this study, we will adapt and test a culturally tailored internet-based smoking cessation (**I-ANBL**) program based on ANBL, for a unique subset of the AI population: students enrolled in tribal colleges/universities.

Primary Aim: To test the effectiveness of a culturally-tailored internet-based smoking cessation intervention (**I-ANBL**) compared to an internet-based heart healthy diet (I-FV: fruit/vegetable) control condition in a randomized controlled trial with Tribal College students. Our hypothesis is that American Indian tribal college students randomized to the culturally-tailored smoking cessation arm will have significantly higher 7-day point prevalence abstinence (defined as no cigarettes in the past 7 days, biochemically verified) rates at 6 months than those receiving the heart healthy diet intervention.

Secondary Aims	Hypotheses
1. To test the effects of the intervention on intermediate smoking variables including number of cigarettes smoked and number of quit attempts at 6 months following randomization.	1. At 6 months following randomization, among those who continue to smoke, participants in the culturally-tailored (I-ANBL) condition will show a greater reduction in the number of cigarettes smoked than participants in the heart healthy diet arm (I-FV).
2. To compare differences between I-ANBL and I-FV in adherence rates to program participation at 6 months following randomization.	2. At 6 months following randomization, participants in the tailored I-ANBL group will have significantly higher adherence rates than smokers in the I-FV group.
Process Objectives	
1. To identify factors that enhance the dissemination aspects of the I-ANBL program.	
2. To evaluate the costs of delivering the tailored intervention.	
3. To examine potential moderators of the intervention and cessation relationship.	

Testing an innovative, culturally-tailored, internet-based intervention will address a critical need in smoking cessation treatment for this high risk group of American Indian Tribal College students. This proposal extends our previous CBPR collaboration with the American Indian community to address the significant problem of smoking and to reduce health disparities in this underserved population.

Tobacco use prevalence in American Indian (AI) adolescents/college students

Among all young adult college students in the US, American Indian tribal college students have the highest smoking prevalence of all racial/ethnic groups. Interventions aimed at reducing smoking among AI college students are limited. Data from the Monitoring the Future Survey show that racial/ethnic smoking prevalence is highest among AI high school seniors (males 41.1%, females 39.4%).¹ In a national study of US high school seniors, AIs reported the highest levels of tobacco, alcohol and illicit drug usage across all ethnic groups between 1996 and 2000.² In a recent survey among South Dakota high school students, more than 56% of AI youth reported they have ever tried smoking. In the same survey more than 28% were current smokers. In a study of 906 public school AIs between 6th and 8th grade, 45% reported current usage of some tobacco product, with 79% having tried a tobacco product. Despite high prevalence rates of AI adolescents, there is little research on initiation patterns and possible socio-cultural and environmental differences that may contribute to smoking initiation.

Importance and need for culturally-tailored smoking cessation for Tribal College Students

Interventions aimed at reducing smoking among AI college students are limited. Culturally appropriate interventions that recognize the historic and sacred nature of tobacco in AI communities are needed to prevent ineffective intervention strategies. AI lands are sovereign

nations and are not subject to state laws prohibiting the sale and promotion of tobacco products to minors. As a result, AIs have access to tobacco products at a very young age. With increasing numbers of AI adolescents attending or expecting to attend and the high prevalence of smoking in this group, it is important to develop and test a cessation intervention. The tribal college environment is the perfect place to test tailored interventions due to the high percentage of AI students and the rapidly increasing nationwide representation of Indian tribes in enrollment.

Disparities in the Health Consequences of Smoking

Cigarette smoking is the number one cause of preventable death among AIs.^{3,4} The death rate among AIs due to tobacco use is double that of other groups in the United States. Two out of every five AI and one out of every two AI smokers will die from tobacco-related diseases if current trend of smoking is not reversed. Cancer is the second leading cause of death among AI and is the leading cause of death among AN. Lung cancer is the leading cause of cancer death for both AI men and women. There is variability in lung and bronchus cancer mortality among Native Americans by region, from 12.9 per 100,000 in Southwest to 93.6 per 100,000 in the Northern Plains, reflecting regional differences in smoking prevalence rate.⁵ The decrease in cancer mortality in the US starting in the mid-1990s did not extend to AI, who experienced increased mortality when comparing 1990-1995 to 1996-2001. Lung cancer mortality during this time period increased from 38.75 to 41.06/100,000. Recent triangulation of cancer data shows much racial miscoding and suggests that incidence and mortality rates for all cancers in AI may be underestimated by as much as 100%.

Cultural Aspects of Tobacco

There is much diversity in tobacco use among AI. Along with such plants as sage, cedar, sweet grass, and red willow bark, tobacco has long been a sacred plant for many AI tribes.¹⁸ Because tobacco was not native to all areas of the US, some tribes did not use it historically. However, early use of tobacco in smoke offerings, pipe smoking, burial services, gift-giving, and for medicinal purposes is well-documented, particularly among tribes native to the eastern seaboard and the Great Plains (e.g. Six Nations of the Iroquois,²⁰ Delaware, Nanticoke,⁶ Lakota⁷). Many AI believe that tobacco connects them to the spirit world through prayer (e.g. Lenape⁸).⁹ Tobacco is also used at ceremonies, such as sweat lodge, Sun Dance, or *Yuwipi* (e.g. Lakota¹⁰) and may be considered a gift from the Creator (e.g. Absarokas and Hidatsa⁹). Traditional tobacco use is common and has diffused to many AI who did not historically use it, particularly at powwows, where it is often given as a gift to the host drum.¹¹ When developing a smoking cessation program for AI, it is imperative to acknowledge the diversity of traditional use of tobacco and its economic importance. It is also important to differentiate between traditional and recreational tobacco use and acknowledge that tobacco control messages that portray tobacco entirely negatively may be ineffective and offensive.¹²

CBPR among AI

CBPR can be defined as “a *partnership* approach to research that *equitably involves*, for example, community members, organizational representatives, and researchers in *all aspects* of the research process and in which all *partners contribute expertise and share decision making and ownership*”(emphasis added).¹³ Key concepts within CBPR that differentiate it from other types of research involve the partnership between the academic institution and the community,

the equitable distribution of all aspects of the research process, and the shared decision making and ownership of data.¹³ CBPR has been used successfully in many ethnic minorities, including AI, where it has been implemented for tobacco research, cancer prevention and control, elder abuse, youth wellness, genetic issues, environmental exposures, and mental health.¹³⁻³⁹ Researchers have called for the use of CBPR in AI communities^{16,17,19,20,29,32,38}, largely due to historic abuses. Burhansstipanov et al. (2005) assert that the majority of AI communities prefer CBPR to other research methods and some communities mandate its use. We use CBPR to guide all of our research, ensuring equal representation of community and academic views throughout the research process and involving community members in all phases of the research process.^{40,41} We also employ AI community members on all projects and report our findings regularly to the community through research forums, a quarterly newsletter, and an annual report.^{40,41}

Internet-based Health Education in AI

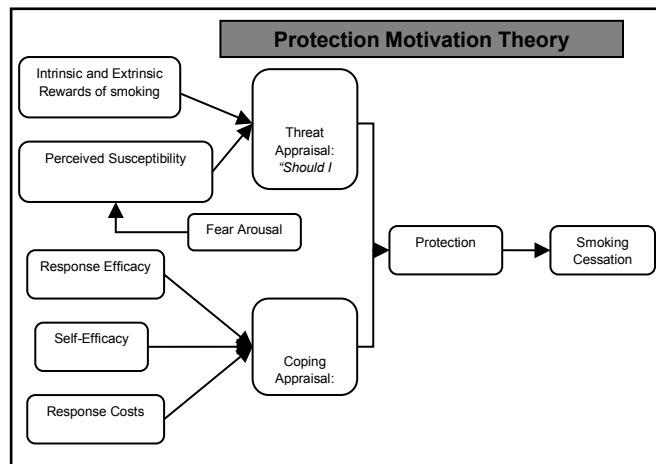
More health education consumers, including AI, are using the Internet for information than ever before, including for information about smoking and lung health, as well as exercise, nutrition, and other health risks.⁴²⁻⁴⁶ Recent findings from the U.S. Office of Disease Prevention and Health Promotion found that in AI communities up to 62% of patients had used the Internet for some type of health education. Our own research has shown that the overwhelming majority of AI in our area use the Internet for health information and they prefer to get health information from the Internet over other sources.^{47,48} The Office of Disease Prevention and Health Promotion recommends using artwork and/or graphics from various tribal regions to promote the traditional belief that artwork can inspire healing.⁴⁹ This recommendation is consistent with our own findings that AI people want visuals and artwork in health education materials and that they would prefer visuals from a variety of tribes rather than “generic” images of AI.^{50,51} Recommendations for the usability of the site are less specific to the population and are focused on ease of use. They include not using a second browser window to display linked sites, not allowing text search results to produce extremely large numbers of resources, being careful of using unfamiliar terminology to label advanced search options, making sure to group information into categories that match user expectations, and providing more instructional content on sites to help users determine where to go to get the information they want.⁴⁹

Theoretical Framework

We will use a theoretical framework that incorporates the principles of CBPR including: 1) tailoring to meet the needs of individuals and communities; 2) involving participants in program development, implementation, and evaluation; and 3) using ecological frameworks that attend to multiple levels of analysis.⁵⁸ To address the first two principles, we involve AI community members in all phases of research. We also recognize that our community is not defined by geopolitical borders, but by a shared identity. This shared Native identity has multiple manifestations that do not form one overarching culture, but rather include multiple cultures of different tribes. Because of this heterogeneity, tailoring interventions to the community or “culture” is difficult. We will address this throughout our program by incorporating ideas and practices from many AI cultures. To address the third principle and to understand the factors affecting tobacco use among AI, we use Critical Medical Anthropology (CMA) as an overarching organizing perspective.⁵⁹ CMA recognizes four levels of analysis as important for any holistic perspective on medical care and encourages studies of health-related issues within

the context of a class-based world system, which in this case includes the history of subjugation and attempted assimilation of AI and their current relationship with the US federal government and the economic role of tobacco in the world system. CMA has been used to study tobacco since the late 1980s,⁶⁰⁻⁶³ calling for the integrated study of the political-economic framework and cultural meaning of tobacco.

To CMA, we add Kleinman's idea of patient/provider explanatory models⁶⁴ and Protection Motivation Theory (PMT)⁶⁵ to guide the intervention at the intermediate, micro social, and



individual levels. Explanatory models can be understood as the way an individual understands a health outcome and its treatment, outcomes, and social influences.⁶⁴ We will address the individual behavior of cessation by incorporating ideas from PMT into our curriculum. PMT includes ideas from the Health Belief Model,⁶⁶ and the constructs of self-efficacy, fear arousal, appraisal, and coping. PMT describes the decision to quit as the result of a combination of threat appraisal and coping appraisal, i.e. “should

I quit” and “can I quit”. Threat appraisal is an appraisal of the rewards of smoking versus the health outcomes associated with it. Fear of these health outcomes is also part of the appraisal. Coping appraisal is an appraisal of response efficacy (e.g. “quitting would be beneficial”) and self-efficacy (e.g. “I am confident that I can quit”) versus the costs of quitting, e.g. withdrawal symptoms. PMT has been used in smoking cessation programs for ethnic minorities^{67,68} and have been used in the AI population for community-based participatory research,^{69,70} substance abuse research,⁷¹⁻⁷³ and CVD research.⁷⁴

II. Results of Similar or Related Studies

Our group has extensive experience conducting tobacco control and health promotion research in a variety of settings, with minority populations, and long-term experience working with the AI/AN population. Below we discuss formative studies directly leading to the development of our current proposal. We then briefly discuss research completed by the Principal Investigators and the co-Investigators, specifically highlighting our work in smoking cessation in the AI/AN population.

Formative Research for this Proposed Study

Our American Lung Association (ALA) funded (SB-11343-N, PI: Choi) formative research addressed the important and neglected public health problem of smoking among AI/ANs. The goal of this project was to identify culturally acceptable and potentially effective methods for smoking cessation in this underserved and high risk population.

Focus Groups: We conducted six focus groups with AI/AN smokers (N=41) at HHC to determine facilitators and barriers to smoking cessation, and the feasibility of developing a smoking cessation program for a heterogeneous AI/AN population. These participants represented 23 different nations.

Participants discussed three major themes: traditional use of tobacco, quitting and quit attempts, and smoking cessation program. We currently have two published manuscripts (see appendix) and two national presentations based on these data. Based on results of these focus groups and meetings with AI/AN community members, we began creation of a culturally-tailored smoking cessation program.

Feasibility/Compliance Pilot: Based on the findings from our focus groups, previous smoking cessation programs developed by members of our team, and the Second Wind program, we began creation of the ANBL program. The pilot version was developed with direct community involvement in an iterative process that included weekly meetings with AI/AN colleagues and community members. It included group sessions and individual phone calls, but used different timing and frequency, as well as a draft curriculum. The name, “All Nations Breath of Life” and slogan, “Light Up a New Way,” were selected from community members’ submissions to a contest. We completed a pilot project to test the implementation feasibility and participant compliance of ANBL at HHC with 30 AI/AN smokers. All participants were offered either nicotine patch or bupropion for free. At the end of the 12 week program, 80% of our participants were smoke free. At 6 months, approximately 25% of the participants remained abstinent (verified through carbon monoxide test). At 6 months, our retention rate was approximately 80% for this pilot. During our pilot studies, we collected data on the characteristics of smokers at HHC.

The results from this initial small pilot study of AI/AN smokers demonstrate our ability to recruit and successfully follow-up participants for a 6-month period to verify smoking abstinence. In addition, these results confirm smoking prevalence findings from other studies that AI/AN smokers are lighter smokers than white smokers in the U.S. Finally, the findings demonstrate preliminary efficacy of our ANBL program.

Evaluation of ANBL Print Materials Using the Suitability Assessment of Materials (SAM):

Internal funding from our institution’s Research Institute (PI: Daley), allowed us to complete a formal assessment of our educational materials for scientific accuracy, readability, and cultural appropriateness. Smoking cessation experts in epidemiology, medicine, and psychology evaluated the content for scientific accuracy. All educational materials were then scored by two members of the research team using the

Suitability Assessment of Materials (SAM) and the Simplified Measure of Gobbledygook (SMOG) reading grade level test. The SAM was developed to allow a full evaluation of print materials for health education in any targeted population and has been validated with 172 health care providers from several cultures, including AI/AN. Twenty-two factors are scored in the areas of content, literacy demand, graphics, layout and topography, learning stimulation and motivation, and cultural appropriateness. Educational materials are given a percent score that can be interpreted as follows: superior (70% - 100%), adequate (40% - 69%), or not suitable (0%-39%). Pilot participants, group facilitators, and CAB members check for cultural-

appropriateness. In general, community members found that ANBL was appropriate, and they provided a number of suggestions for improvement that have been incorporated into the next version of the curriculum. Our materials were found to be scientifically accurate and culturally appropriate. The mean SAM score was 80% and the average reading grade level was 7.1. Our assessment results have produced one manuscript⁵² and one national presentation.

To further check cultural appropriateness, our AI/AN program facilitators and pilot participants were asked to comment on the curriculum, and a series of semi-structured interviews (N=6) were conducted with AI/AN community members, who were chosen for their familiarity with traditional use of tobacco and affiliation with different nations. Interview participants were asked to comment on the cultural appropriateness for the AI/AN population, as well as ways in which the materials could be improved. In addition, they were asked to provide us with information about traditional use of tobacco in their nations. These results were published and presented at a national conference on Nicotine and Tobacco Research.

These preliminary findings are important because the results confirm both the cultural appropriateness and readability of ANBL materials. In addition, these findings also verify the scientific accuracy of the ANBL materials.

Pilot Feasibility of ANBL in Urban and Reservation based Tribes in Kansas

Our American Cancer Society (RSGT-06-260-01-CPPB; PI: Choi) funded grant is a 3 year pilot/feasibility study of ANBL with all program components. The ANBL program components include an initial individual session along with 8 weekly group sessions with individual telephone calls between the group sessions. During the previous pilot, we conducted the ANBL program with 5 weekly in person sessions and another version with 8 weekly in person sessions. The overwhelming preference from our participants was for the more intensive 8 weekly in-person group sessions. All of our participants expressed the need to maintain the group support and dynamics in order to maintain long term abstinence. As a result, we decided to implement the 8 session version rather than the smaller number of sessions. This larger pilot study started in 2006 and we have completed 10 groups of AI/AN smokers. In addition to the ANBL program, all participants were offered varenicline as a form of pharmacotherapy. In this pilot, we also added the use of motivational interviewing (MI) counseling throughout the individual phone sessions. Recruitment and retention (approximately 80%) has been very successful. All participants completed surveys for each group session and there have been no refusals among those in attendance. For the first time, we have also collected saliva samples from our participants at baseline, week 12 and 6 months to verify smoking status. The six month smoking abstinence rates are approximately 30% with ANBL in combination with varenicline. Our dropout rates for this larger feasibility pilot study have been between 15-20 % at 6 months.

These results demonstrate our team's ability to recruit both urban and reservation based AI/AN smokers in the region. In addition, we have successfully shown our team's ability to maintain high recruitment and retention rates for the groups of smokers for the high intensity ANBL program. We have also successfully integrated the use of MI counseling during the individual phone calls and demonstrated acceptance in this population. Our current version of ANBL is more intense compared to the first version of the program. This increase in intensity is a result of participant and facilitator feedback that 5 in-person group sessions was

insufficient and that increasing the in-person group sessions, as well as adding the brief MI telephone sessions helped them maintain abstinence throughout the program.

Using Web-Based Interactive Technology with AI

(SB-40588-N:PI Daley) We conducted a cross-sectional survey (N=998) that focused on health behaviors and health information seeking. Our results showed that 48% of AI men and 68% of AI women in our region use the Internet for health information. We also found that AI smokers who use traditional tobacco are statistically significantly more likely to remain quit for one year later. We conducted focus groups (N=204) and we found that students use the Internet more often and for more different tasks. Participants wanted more culturally-tailored websites specific for AI and their health concerns. This project also allowed us to develop and assess a culturally-tailored, interactive, multi-media website to accompany ANBL, using assessment methods similar to those proposed in this project. This project also included the development of a full-length (30 minute) video about traditional tobacco video and development of a full-length (30 minute) video about smoking facts for AI.

These results demonstrate our teams ability to engage AI/AN in using web-based interactive technology. In addition, we have shown that AI/AN students use the Internet more often than others and use the Internet for health information.

Understanding Smoking among Tribal College Students

(P20-NIMHD: PIs: Daley & Choi) We are conducting a longitudinal web-based survey of tribal college students at two tribal colleges on behavioral risk factors including smoking. We have found that approximately 40% of tribal college students are current smokers (Freshmen = 36%, Sophomores = 40%, Juniors = 45%, Seniors = 27%).

This study demonstrates our team's ability to successfully work with tribal colleges and recruit tribal college students to participate in research studies.

Summary

In conclusion, these preliminary studies have: 1) demonstrated our successful collaboration and commitment to the AI/AN community; 2) shown our experience in conducting smoking cessation studies; 3) confirmed the cultural-appropriateness of ANBL; 4) shown that the ANBL approach is feasible and acceptable in the AI/AN population; 5) proven our ability to successfully recruit AI/AN smokers for a pilot cessation study; 6) demonstrated our ability maintain excellent retention rates (approximately 80%); and 7) demonstrated preliminary success of smoking abstinence with ANBL. Collectively, these results position us well to undertake this randomized clinical trial that we will now propose in the next section.

III. Benefits and Risks of Research

Benefits

The participants will have the opportunity to benefit by making behavioral changes in their smoking or by stopping smoking. Participants who stop smoking will experience invaluable

health benefits, and family members of participants who stop smoking would be expected to benefit from reduced exposure to second-hand smoke. Participants will receive several things to help them quit smoking, including the opportunity to receive free NRT, Chantix® and NRT or Zyban®, materials to assist with quitting smoking, web-based culturally tailored smoking cessation counseling. Participants will have an opportunity to receive \$90 in gift cards for recognition of time and trouble spent participating in this study. Additionally, participants will receive incentives valued at approximately \$30 per person. Participants will be informed that disbursement of the incentives is not contingent on their smoking status.

Despite over two decades of intensive tobacco control efforts, about 23% of Americans continue to smoke. Native Americans carry a disproportionate burden of tobacco use and related mortality. Racial disparities in tobacco use and cessation translate into higher rates of mortality from tobacco-related disease. Thus, to address the tobacco use epidemic and its consequent health impact, there is an urgent need to test interventions for tobacco dependence, to improve delivery by individualizing treatment based upon smokers' needs, and to reduce barriers to smoking cessation in underserved populations. This study will assess whether a culturally targeted smoking cessation program with choice of pharmacotherapy is effective for smoking cessation among AI tribal college student smokers. The knowledge to be gained from this research could potentially change the types of treatment offered to AI college student smokers. The risks involved in gaining this knowledge are reasonable given the potential impact of the knowledge to be gained on smoking cessation treatment.

Risks

Most of the risks involved in the study relate to adverse events related to study medication. Chantix and bupropion are both approved by the Food and Drug Administration as an aid for smoking cessation. The most common adverse events associated with bupropion are headache, insomnia, rhinitis, dry mouth, and anxiety. Bupropion is associated with an increased risk (1/1000 at 300 mg/day) of seizures (GlaxoSmithKline, unpublished data). We will minimize this risk by screening out and preventing participants from using bupropion who are also currently using any additional form of bupropion, psychoactive medications, nicotine replacement therapy, fluoxetine, clonidine, buspirone, or doxepin in the past 30 days and those with: self-reported alcohol dependence within the past year; history of seizures or head trauma; history of bulimia or anorexia nervosa; pregnant (as measured by over the counter pregnancy test kit for women of child-bearing age only) or contemplating pregnancy; breast feeding; myocardial infarction in the past 30 days, and use of other forms of tobacco in the past 30 days. The most common adverse events associated with Chantix are nausea, changes in dreaming, constipation, gas, and/or vomiting. The FDA recently required new boxed warning for both these medications: people who experience any serious and unusual changes in mood or behavior or who feel like hurting themselves or someone else stop taking the medication. Chantix has no clinically meaningful drug interactions based on drug characteristics and clinical experience with the drug to date (Pfizer).

All participants requesting prescription medications, Chantix or Bupropion will be screened and medically cleared by the on-the-ground primary care physician. Dr. Greiner will continue his role as reviewing study physician. Dr. Greiner will provide secondary review of all screeners, and intake materials to make sure there are no contradictions to pharmacotherapy. We have a long track record of Dr. Greiner reviewing all medication screeners and study documents on

participants in our tobacco cessation studies. We are comfortable with individual's self-report, mostly because we have done this successfully for years in our other tobacco cessation studies.. For Participants at a Tribal college: Participants who choose to take Chantix will also be monitored by Tribal clinic, will correspond with Dr. Greiner about participants taking Chantix. All Participants will be prompted to discuss any side effects prior to starting each web-session and will be given the study office phone number (24-hour coverage) to contact study staff and/or the investigators to report adverse events. On – the – ground physician will decide if they need to directly communicate with participants when participants initiate or while they are taking medications. Our staff will also have weekly contact with participants (via our web-based communication system). Dr. Greiner will provide secondary review and communicate with the on-the-ground physician or participant if need clarification on any screener responses, if the participant reports side-effects from study medications, if the participant has an Adverse Event (AE) that could be due to study or study medication related, or if the participant requests to speak with a study physician. We will follow the NIH guidelines for reporting adverse events to the Human Subjects Committee. Any problems needing medical attention will be referred to Dr. Greiner (consulting physician) and the patient's personal physician. The study medication will be discontinued in patients who become pregnant, report use of any other medications that contain bupropion (e.g., Wellbutrin), or develop a contraindication. Patients will be instructed not to smoke cigarettes during treatment. Women of child bearing age who are participating in the program and requesting to use Chantix or Zyban will agree to use a form of birth control during the course of the study.

Alternatives to participating in the study are to quit cold turkey, use other smoking cessation programs, purchase nicotine gum or patches from the pharmacy, obtain a prescription for bupropion or other smoking cessation products from their physician, or continue to smoke. Other risks for participating in the study are minimal and include those associated with the inconvenience of completion of several questionnaires, email follow-up assessments, and the inconvenience of logging onto the internet for web-based counseling sessions.

All participants in the study will be quitting smoking. Risks to all participants will be minimized through frequent monitoring through the web chat portal where participants can chat with study personnel. All participants will be given detailed instructions on how to use either the nicotine replacement therapy, Chantix or bupropion prior to distributing the cessation aids. Finally, all participants will be given a 24 hour monitored telephone number to contact in case of adverse reactions to any of the cessation aids that they are using.

Furthermore, KUMC will be in weekly contact with a clinician or nurse at the Tribal campus health center to review any adverse events or suspected adverse events. We will also be specifically asking participants about adverse events on a weekly basis (via our web –based communication system) and follow-up with phone calls to review anything reported. The following questions will be asked from participants using web-based system to report any adverse events from medications:

- “Have you had any side-effects from your pharmacotherapy this week?”
- “Have you had any urgent or emergent visits to the doctor or a hospital for health problems this week?”

- “Have you had any new unexpected health problems this week that we have not talked about?”

IV. Inclusion/Exclusion Criteria

Eligibility

The eligibility criteria listed below will be assessed at the recruitment visit.

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> ◆ Age 18 years or older ◆ Currently enrolled at a Tribal college ◆ Have a valid telephone number and email address ◆ Willing to participate in all study components ◆ Willing to be followed-up for 6 months ◆ Self identifies as American Indian or Alaska Native ◆ Is a current smoker – self defined 	<ul style="list-style-type: none"> ◆ Planning to leave the college within next 6 months ◆ Medically ineligible as a result of screening questions

Medical Exclusion Criteria
<p>For overall participation</p> <ul style="list-style-type: none"> ◆ Medically ineligible as a result of screening questions ◆ Participant under the age of 18 years
<p><u>For NRT (Patch, gum, lozenge):</u></p> <ul style="list-style-type: none"> • History of severe eczema or any serious skin problem if requested nicotine patch • History of severe allergic reaction to the nicotine patch or other skin adhesives • History of heart attack in the last 2 months • Currently experiencing frequent angina or chest pain related to heart • Currently experiencing signs and symptoms of peptic ulcer • Currently receiving medications for rapid or irregular heart beat • Currently experiencing signs and symptoms of severe, uncontrolled high blood pressure <p><u>For Chantix:</u></p> <ul style="list-style-type: none"> • Pregnant or breast feeding or planning to become pregnant in the next 6 months • Currently using nicotine replacement therapy (NRT) • History of suicide attempt in the past 12 months

- History of thoughts of suicide in the past 12 months
- History of thoughts of harming others in the past 12 months

For Zyban:

- Pregnant or breast feeding or planning to become pregnant in the next 6 months
- History of seizure disorder or head trauma
- History of severe allergic reaction to Zyban (also known as Wellbutrin, Bupropion)
- History of eating disorder, such as anorexia or bulimia, which is overeating and throwing up
- Currently taking Wellbutrin, Zyban or any other medications that contain bupropion
- History of alcohol or substance abuse in the past year
- Current excessive alcohol consumption defined as 14 or more alcoholic drinks per week and / or binge drinking (5 or more drinks on one occasion) 2 or more times in the past month
- Use of MAO inhibitors, such as Nardil, tranylcypromine, phenelzine, or Parnate
- Reported use of illegal drugs (opiates, cocaine, narcotics, or other stimulants such as diet pills)
- Use of psychoactive medications, such as fluoxetine, doxepin, clonidine, or buspirone
- Use of benzodiazepines, such as Xanax, Valium, Ativan, Klonopin in the past 2 weeks

V. Study Procedures

Design Overview

The proposed study is a randomized design in which Tribal College smokers will receive one of two internet-based interventions: 1) a culturally and individually tailored, interactive smoking cessation intervention (**I-ANBL**); or 2) internet-based healthy diet -fruit and vegetable consumption intervention (**I-FV**). Participants in both groups (I-ANBL and I-FV) will be offered pharmacotherapy (e.g. varenicline or bupropion or NRT). The primary outcome of interest will be biochemically verified continuous abstinence at 6 months. Secondary endpoints include number of quit attempts and number of cigarettes smoked (among continuing smokers), pharmacotherapy utilization, and the number of completed web-sessions. We will also examine the marginal cost-effectiveness of the intervention.

We propose the adaptation and testing of a culturally tailored smoking cessation program for tribal college students. We will finish developing the program using an iterative, CBPR process that we have used in the past to develop a successful smoking cessation program for AI.

The study will be done in three phases over a five-year period. Phase 1 will include adaptation of the program and tailored materials, including assessments of the website for scientific

accuracy, readability, cultural appropriateness, and navigability; Phase 2 will be to conduct the randomized trial and Phase 3 will consist of data analysis and dissemination.

Participants will be recruited from a Tribal college.

Pharmacotherapy: The PI of this study along with our AI community members agreed that all participants (I-ANBL and I-FV arms) had to be offered pharmacotherapy (varenicline or bupropion or NRT) as a component of the study design. This decision was a collaborative one between the AI tribes and the investigators who have worked with this population. The AI community will not accept placebo treatment, therefore, the interventions would not be acceptable or feasible to potential participants if a placebo was part of the study design.

Implementation Plan

The project will be implemented in three phases over five years, as summarized in the table. The main purpose of this study is to determine the effectiveness of an internet-based culturally-tailored smoking cessation program for tribal college smokers.

Phase 1: Development and Training	Development and assessment of interactive website; training of staff; focus groups and pre-testing, conduct meetings with CAB, submit any protocol modifications for community and IRB approval	Year 1
Phase 2: Deliver Intervention	Recruitment of tribal college smokers into study, baseline measurements, randomization of eligible students, implementation of internet-based intervention, follow-up, preliminary data cleaning, and initial data analysis	Year 2 – Year 4
Phase 3: Data analysis and dissemination	Post-intervention assessments; final data cleaning and analysis; manuscript preparation; presentations to communities and at professional conferences	Year 5

Phase 1: Development and Training

This phase includes conducting focus groups with tribal college smokers to obtain input on issues related to the internet based culturally-tailored program. Finalize development and assessment of interactive website. In addition, we will also develop strategies related to recruitment, study participation, and training of AI research staff. These smokers along with the Community Advisory Boards will also assist in finalizing and pilot testing the website and will play a strong role in the recruitment, retention, implementation, and dissemination of the proposed project.

Focus Groups: Sampling Frame & Recruitment- We plan six focus groups, three males and three female groups. We stratify by gender because, based on preliminary data, we learned that there are differences in smoking by gender. Because the Internet is a key aspect of our program, we need information from students to ensure we meet the needs of these participants. We plan 3 focus groups per stratum, but will assess saturation after conducting the focus groups and will

cease recruitment if our data are saturated. We plan for 10 participants in each focus group, for N=60.

Development of Moderator's Guide: Dr. Daley will lead focus group moderator's guide development based on an examination of ANBL. Guide will be developed with Native team members and CABs and will be modified for each stratum. We will cover the following: previous experience with quit attempts, how smoking is similar to/different from cigarettes and traditional tobacco, and program development.

Focus Group Procedures: Focus groups, lasting approximately 60 to 90 minutes, will be conducted at a variety of times to allow for participation of individuals with different schedules and will be audio-taped and transcribed verbatim. Focus groups will be moderated by ethnically and gender-matched research assistants who have been trained to conduct focus groups by Dr. Daley, who will observe a minimum of 2 mock groups by each research assistant prior to allowing them to conduct groups. We have found that matching ethnicity when selecting focus group moderators is imperative to gaining richly detailed information. Prior to the start of the group, participants will provide written and verbal informed consent. Participants will receive a \$25 gift card and meal for their time and participation.

Digital Recordings:

All digital audio files will be housed on a secure network drive at the University of Kansas Medical Center after transcription and will be destroyed at study conclusion in 5 years. Transcripts and surveys will be kept in a locked file cabinet at the Center for American Indian Community Health. Transcripts will not be identified by name and no quotes will be attributed to any individual in any presentation of the data. The digital recordings will be labeled by unique participant identification numbers that will not be linked to any personal information. Data will be presented in an aggregate form, as well as with individual quotations, without identifying information.

Focus Group Analysis: Dr. Daley will lead all analysis based on a CBPR approach developed by this research team. Text analysis will follow a grounded theory approach and will use techniques developed by the PI during analysis of qualitative data from previous work with community. In grounded theory, categories and concepts emerge from the text and are linked to formal theories. Using this approach will allow us to develop a more accurate theoretical framework and model of behavior. Analysis techniques follow a series of steps based in CBPR and ethnography and include five analysts, three coders and two reviewers of themes. Both scientists and community members are included in the coders and reviewers. Analytic coders read through the transcripts and inductively come up with topic areas. The coders meet and develop an initial code book based on these topics. Coders then reread transcripts, beginning deductive coding with the code book and including any inductive coding necessary to complete topic areas. Coders meet again to finalize the code book and then reread the transcripts, completing all deductive coding. Coders meet a third time to discuss themes, coming up with basic ideas about thematic statements, which are then drafted by the primary coder (scientist) and sent to the secondary coder (community member) for review. Coders meet a final time to reach a consensus on the thematic statements before they are sent to the emic and etic reviewers, who discuss the themes and come up with finalized statements that are brought to the full analytic team for consensus.

Navigability of website: We plan a series of 20 semi-structured interviews with AI smokers, 10 college male students and 10 female college students, to understand the navigability of the program website.

Because using our website is crucial to program success, we believe we need to test navigability with individuals who would be potential participants. Recruitment will follow a similar approach to recruitment for focus groups and other interviews. During each interview, participants will be asked to perform a series of activities on the website designed to test the difficulty each participant has in finding different information and interacting with the site (*see table - right*). Participants will also be asked a series of open-ended questions about the site and will be given additional time to “play” with the site and provide input.

In addition to our formal assessment, all members of the research team will try all navigation links within the site in an attempt to “break” it. Each time problems are found, they will be corrected. We have used this technique successfully in the past to develop multiple websites.

Phase 2: Delivery of Interventions

The objectives of this phase are to: (1) recruit and screen participants for eligibility into study; (2) randomize tribal college students into the two arms (**I-ANBL** or **I-FV**); and (3) implement interventions and follow-up. We will recruit and randomize 300 tribal college smokers into two groups – the culturally-tailored arm (**I-ANBL** + offered varenicline/bupropion/NRT) and the heart healthy arm (**I-FV** + offered varenicline/bupropion/NRT).

Tribal College Student Recruitment

As has been done previously, we will follow CBPR methods in that the leadership and administration will be involved in recruitment of smokers. We have a very strong track record

Possible Interview Tasks	
Finding Information	
	What you currently see is the home page for our quit smoking program. Please find the page that has facts about what smoking can do to your health and identify the different types of cancer that can be caused by smoking
	Please find the login for program participants. Once you find the login, I will give you a guest login so that you can see additional parts to the site that are meant for program participants.
	Within the participant site, please find the educational brochure for session 4: Traditional Use of Tobacco.
	Within the participant site, please find the announcement board for group 5. Are there any current announcements for this group?
	Within the participant site, please find the calendar of events for session 5. When is the next session?
Providing Information	
	What you currently see is the home page for our quit smoking program. Please find the page that allows you to submit your name for more information about the program and submit it.
	Please find the page that allows you to post a question to be answered by our staff and post something.
	Please complete the on-line survey about health effects of smoking and tell me what the graphic pie charts that pops up after you answer says about how others have answered.

with a few Tribal colleges on multiple initiatives to improve the health of both students and faculty at the tribal college. We will employ multiple recruitment strategies as we have done on previous projects and health activities. We will advertise on campus with both flyers and on their school website, in classrooms during both class and new student orientation, social media sites such as Facebook, and Native publications at the Tribal colleges. We have employed many graduates of tribal colleges who have established strong relationships with faculty and administration, which will provide consistency and a recruitment team well-experienced on study requirements. We will have no problem recruiting 242 smokers over 3 years of the study. To account for potential attrition, we will recruit a total of 300 smokers and assume a 20% attrition rate.

Eligibility Requirements

We will recruit a total of 300 tribal college students who are current smokers (smoked at least 1 cigarette in the past 30 days), at least 18 years of age, valid telephone number and email address, willing to be followed-up for 6 months, and willing to participate in all study components. Students who are planning to leave the university within next 6 months or who are medically ineligible after screening will be excluded from the study.

Annual number of students	Adjust for smoking prevalence * (40%)	Adjust down 50% for refusals	Adjust down 20% for no-show to enrollment	Targeted Total enrollment over 3 years
1,200	480	240 eligible	192 per year	300

We will recruit 14 students per month so that the process of medical screening for pharmacotherapy is not a burden on the on –the-ground physician and the research staff.

Program Development: I-ANBL

We anticipate four primary components to the program, which will be designed by our focus group participants, CAB members, and Native team members, including: the I-ANBL Interactive website, an educational curriculum, pharmacotherapy, and participant incentives, all of which will be tailored to a heterogeneous group of AI tribal college students.

I-ANBL Interactive Individual Sessions

In order to deliver personalized and individually-tailored intervention, we will include three inter-related components: 1) a web screening instrument to measure demographics, health status, smoking status, health behaviors, behavioral determinants, and level of motivation and confidence, 2) a message source file that contains all tailoring messages and a, 3) computer program that offers the possibility to analyze the screening results and to select the correct message from the message source file.

Development of the Internet site will be led by Ronnie Raney, programmer at KUMC with whom we have worked on several projects and who developed the current ANBL

(www.anbl.org), CAICH (www.caich.org), and AIHREA (www.aihrea.com) websites. We will follow all guidelines for the development of Internet sites for the AI/AN population set forth by the Office of Disease Prevention and Health Promotion discussed in the background section. We will also follow all guidelines set forth by our focus group participants and our CABs.

Programming will be done using the Adobe Creative Suite® and Moodle CMS™. These are software programs designed to assist in the development of Internet sites with which the PI and web designer have experience. The website will have a patient portal that participants will log into. All participants will have an individual section in their portal in which they will enter survey data and can request private on-line chats with our research assistants. Participants will not have access to anyone else's information nor any personal information from an individual.

Computer expert system feedback reports will be based on participants' responses to survey data and include information on: 1) current stage of motivational readiness for smoking cessation; 2) increasing self-efficacy (i.e., confidence) for remaining smoke free; 3) cognitive and behavioral strategies associated with abstinence (processes of change); 4) how the student compares to prior responses (progress feedback); 5)

How the student compares to individuals who are abstinent (normative feedback); 6) maintenance of smoking abstinence. The computer expert system will draw from a bank of several hundred messages addressing different levels of cultural, psychosocial, and environmental factors affecting smoking cessation. Intervention participants will also receive tip sheets addressing barriers specific to American Indian smokers and quitting (as identified during our formative research and Phase 1 of the study).

Educational Curriculum: We will adapt the ANBL materials for the tribal college population through the planned focus groups in Phase I of this study. Previous participants in formative research have stressed that cultural issues must be ingrained within the program and its accompanying education materials, not given "lip service" by putting pictures of AI people on otherwise "white" materials. We will continue to follow this guideline as we modify the materials. We will begin our educational materials modification with our current educational materials for ANBL (*see appendix*). Topics will be modified based on student input.

Pharmacotherapy: Pharmacotherapy is recommended for smokers trying to quit. We plan to give participants in our cessation program a choice of varenicline, bupropion, nicotine replacement therapy or no pharmacotherapy. We choose to give our participants a choice because our experience shows that we would be unlikely to recruit AI participants into a trial that requires pharmacotherapy use. Many AI are unwilling to use Western pharmacotherapy at all and others are unwilling to participate in a "drug trial", particularly if randomization is involved. All participants requesting pharmacotherapy must be medically cleared prior to receiving it.

The prescription medications (Chantix and Bupropion) and over-the-counter NRT (patch, gum, and lozenge) will be stored at KUMC in locked cabinets. KUMC will be responsible for mailing requested medications to the Polson Tribal Clinic in Polson, MT. After getting medical clearance from on-the-ground physician, participants will pick up a one month supply of study medication at the clinic. All the participants will be monitored weekly via web based system for any potential adverse events.

Participant Incentives: Incentives will be identified by focus group participants, CAB members, and Native research team members. For ANBL, we have used things like quit kits (hard candy, toothpicks, etc.), stress balls, flute music CD's for relaxation, and Rez-robics® (aerobic dance videos that include pow wow and traditional dance), among other things. We will provide participants with gift cards for participating in the research. At baseline, we will give participants \$20 gift cards for survey participation. At 12-weeks and 6-months, we will give participants \$40 gift cards for survey participation. We will also give participants a \$10 gift card for providing saliva for cotinine analysis at the time points above. In addition to the above incentives, participants will also receive a \$10 gift card if they complete at least 5 of the weekly web sessions. If the participants complete all 8 weekly web sessions they will receive a \$20 gift certificate. All participants will be asked to provide saliva at baseline, 12-weeks, and 6-months. We ask for repeat samples from all participants for two reasons: (1) nicotine metabolism of smoking has not been previously examined and we plan to look at decreases in use, as well as quitting; and (2) we do not want some participants to be able to obtain additional incentives because we do not want to bias our results. We do not anticipate a problem with participants' willingness to provide saliva; our ANBL programs have a 100% participation rate in this, even though it is voluntary for participants to provide saliva.

Anticipated Flow of Participants:

Telephone Eligibility Screening Interview		
↓		
In-Person Randomization Visit (n=300)		
Web-based weekly		
Sessions	I – ANBL (n=150)	I – FV (n=150)
1	Preparing to quit, pharmacotherapy/nrt, why do people smoke	Assessment of Risk for Heart Disease, pharmacotherapy/nrt
2	Cigarette smoking and Native people, Quit smoking date	Increasing fruit and vegetable consumption, Quit smoking date
3	Coping with Withdrawal	Physical activity
4	Traditional use of tobacco	High blood pressure
5	Stress reduction and relaxation techniques, traditional meditation techniques	Salt and sodium intake
6	Weight management, Healthy American Indian foods, exercise	High Cholesterol
7	Friends and family and quitting smoking, social support	Maintaining healthy weight
8	Staying quit – congratulations Long term maintenance	Low cost healthy eating – fruits and vegetables
Email reminders will be sent before each session so that participants will log in at the appropriate time		
12	End of pharmacotherapy treatment, feedback of program	End of program, feedback

Email reminders will be sent before each session so that participants will log in at the appropriate time		
Month 6	Assessment for current smoking status	Assessment of current smoking status

(Detailed descriptions of the weekly I-ANBL web materials are included in the appendix: will be adapted to integrate tribal college student issues identified during Phase 1 of the study)

- Telephone Screening Intake:** Research Assistants will review inclusion/exclusion criteria, smoking status and basic information about the program. We will not exclude participants who use other forms of recreational tobacco (eg – smokeless tobacco) because, based on our preliminary data, we would be excluding eligible participants if we did so. In addition, community members have encouraged us to be more inclusive for acceptability of the research in the community and make the inclusion criteria less restrictive. Therefore, we will examine use of other tobacco products in a secondary analysis. We estimate screening intake to take 10-15 minutes.
- Individual In-Person Visit (Randomization):** Potential participants will meet with a research assistant on campus. At this initial in-person visit, the research assistant will have randomization assignments with them so they can inform the participant which arm they have been randomized to for this program. This session will allow research assistants to explain the program and answer any questions the participant may have that he or she may have about the program. Informed consent will also be obtained during this visit. Finally, it allows the research assistant to explain NRT or pharmacotherapy and provide each participant with information. Individuals who consent to participation will be enrolled in the program and will remain in the arm to which he/she is randomized to for the study. Research assistants will collect baseline saliva sample from each participant. Participants will be informed for future samples (week 12 and month 6), we will request mailings of saliva samples so they will be taught how to provide such samples at this baseline visit. Saliva sample kits will be provided via overnight mail with a pre-paid overnight return. Members of our team have used this approach in other phone-based smoking cessation programs with success. Participants will be asked to make a decision about NRT or pharmacotherapy prior to the second web session. Facilitators will answer any questions the participant has and participants will be given the option of having the study physician call them to discuss personal concerns. Estimated time for individual session is 50-60 minutes. Participants who have not yet decided on medication will be asked to do so then. All participants requesting any form of pharmacotherapy will complete the corresponding medical screener. The study physician will review all medical information prior to the first session. After taking part in the initial session, participants will be e-mailed a login to the website prior to their first session. Future surveys will be done via web interface.
- Internet Session 1:** Participants will be asked to log into the website prior to the first session to allow for any problems with the site to be fixed prior to sessions starting. Participants who decide to take any study medication will need to visit the Polson Tribal Clinic in Polson, MT to pick up a one month supply of study medication. Any unused NRT or medication will be dropped off at the clinic and then mailed back to the research assistants by the clinic staff. The study physician will be available to answer additional

questions. Beginning with this session and continuing through all sessions. Topics we anticipate covering include, but are not limited to: preparing to quit, dealing with cravings, support systems, traditional tobacco, stress reduction, weight management, and staying quit, along with other topics determined during program development. For each session, the tribal college student will begin the session by answering a series of questions to produce an individually-tailored report that will be provided on the screen at the end of each week's session so that the smoker can work on strategies during the week before the next internet session. Estimated time for the web session is 30 minutes.

- **Internet Sessions 2-8:** *The second session is the quit date for all participants in the group.* Weekly procedures will follow the same format as for the first session. At the session dealing with traditional tobacco, participants will be asked to talk about their own use, though they will not be required to do so because this is not always culturally appropriate. Participants will be asked to fill out weekly brief surveys about their use of tobacco during the week; e-mail reminders will be sent. Participants will also be asked to fill out brief session evaluations on-line after each session; e-mail reminders will be sent for these as well. Session evaluations will go directly into a separate database that will be de-identified; participants will be told about this database to encourage more truthful responses.
- **Weeks 9-11:** Participants will receive one individual email per week from a research assistant.
- **Final Session- End of Treatment (Week 12):** Session content procedures will follow the same format as for other sessions. All participants, regardless of smoking status will receive a certificate of achievement for completing the program and will be asked to submit a saliva sample.
- **6-Month Follow-Up:** At 6-months post-baseline, participants are asked to take part in a final internet session and will receive a \$20 gift card for participation. They will be asked about their smoking status and will be asked to submit a saliva sample. Participants who do not report abstinence from smoking use will be asked if they would like to participate in the full program again. If they choose to participate a second time, they will not be included in *study outcome* measures, though we will track their success. This is done to mimic the real-world situation where a program could be repeated. After the 6-month follow-up, participants will be sent a final anonymous survey about the program via e-mail.

Fruit/Vegetable Consumption (Heart Healthy Diet): I-FV

For the second arm of this study, we will use a culturally-tailored program developed specifically for the American Indian population to reduce their risk of heart disease, "*Honoring the Gift of Heart Health*." We will obtain copyright permission and modify the materials used in this program by removing the information related to smoking cessation for one of their sessions. These sessions help American Indians learn about what they can do to prevent heart disease. We will emphasize the increase consumption of fruits and vegetables as well as addressing other heart healthy activities. *Honoring the Gift of Heart Health* is a user-friendly program developed especially for American Indians. The manual provides the "how-to" for leading group education

sessions. It offers "hands-on" activities that help people build the skills they need to make simple, practical, and lasting changes to help them fight heart disease. The protocol will follow procedures as the I-ANBL arm, however, this fruit and vegetable arm will not include individually tailored components, but just interactive web-based materials related to increasing heart health, including certain activities.

Measures

Schedule of Assessments: The table below represents our preliminary listing of outcome assessments, based on measures used for ANBL and preliminary discussions with community members. During year one of the project, we will work closely with our community partners to refine all measures and potentially add or subtract some of them. Our community partners will have final say on all measures to be used, including whether we use standard measures validated in other populations or modify for our community.

Measures Week	1	2	3	4	5	6	7	8	12	6 mo
Primary Outcome										
The primary endpoint for the study will be biochemically (salivary cotinine) verified point prevalence abstinence, defined as no smoking for the previous 7 days, at the 6-month follow-up. This definition is based on recent consensus statements from the Society for Research on Nicotine and Tobacco Subcommittee on Abstinence Measures.	X								X	X
Biochemical Validation	X								X	X
Pharmacotherapy Use		X	X	X	X	X	X	X	X	
Demographics Tribal affiliation, age, gender, marital status, income, year in school	X									
Smoking behavior										
Traditional use of tobacco	X	X	X	X	X	X	X	X	X	X
Smoking history (age of initiation)	X									
Quitting history (length of most recent quit attempt, number of quit attempts in the past year)	X									
Self-reported Smoking status (number of cigarettes/day)	X	X	X	X	X	X	X	X	X	X
Nicotine Dependence - The Fagerstrom Test of Nicotine Dependence will be used to measure nicotine dependence. ⁷⁷	X								X	X
Self-efficacy	X			X				X	X	X
Motivation	X			X				X	X	X
Environmental factors										
Household structure	X								X	X
Social support	X								X	X

Exposure to others who use tobacco in any form	X			X		X			X	X
Exposure to tobacco marketing	X			X		X			X	X
Psychosocial factors										
Depression using the CES-D, 10-item. ⁷⁸	X		X		X		X		X	X
Negative Affect from the <i>Positive and Negative Affect Scale (PANAS)</i> , ⁷⁹	X		X		X		X		X	X
Nicotine Withdrawal using the <i>Minnesota Withdrawal Scale (MNWS)</i> ⁸⁰	X		X		X		X		X	X
Craving using the <i>Brief Questionnaire of Smoking Urges (QSU-Brief)</i> , ⁸¹	X		X		X		X			
Treatment Factors										
Satisfaction with interactive website					X				X	X
Satisfaction with session topics		X	X	X	X	X	X	X	X	
Satisfaction with session educational materials	X	X	X	X	X	X	X	X	X	
Satisfaction with cultural appropriateness of program	X	X	X	X	X	X	X	X	X	
Frequency of usage of website	X	X	X	X	X	X	X	X	X	X
Consumption of Fruits	X		X		X		X		X	X
Consumption of Vegetables	X		X		X		X		X	X

Process Measures and Evaluation: We plan a detailed process evaluation, with two primary methods, individual surveys after each internet session and surveys after the close of the study. Individual session surveys will focus on content and cultural appropriateness of the session and will include 5-point Likert scale questions and open-ended questions to provide both a quantitative measure of the sessions for comparison among sessions and a qualitative measure for depth of understanding. After the 6-month follow-up, participants will be surveyed individually through the website regarding program exposure and dose: how much of the curriculum materials they used, and how much, if any, pharmacotherapy was used. Participants will also be asked to rate program components overall on a five-point Likert scale for perceived helpfulness, satisfaction, and cultural attentiveness/sensitivity. To assess acceptability, the question commonly used is, “Would you recommend this intervention/program to another friend/relative etc. who smokes?” We will also collect information related to the indicators of feasibility including monthly recruitment rates, retention rates, and frequency of use.

Phase 3: Data Analysis and Dissemination

The objectives of this phase are 1) to conduct data analysis and 2) to disseminate the program.

In Year 5, we will complete post-intervention assessments, data analyses and report writing.

Process and outcome data will be presented at scientific conferences and manuscripts will be submitted to peer-reviewed scientific journals. Ultimately, we envision that **I-ANBL**, if efficacious, could be disseminated and

used as a culturally tailored smoking cessation intervention that could be adopted across different tribal colleges.

Sample Size and Power: The primary endpoint will be cotinine verified 7-day point prevalence abstinence at Month 6. Per preliminary findings, we expect a 30% cessation rate in the **I-ANBL** arm and a 15% cessation rate in the **I-FV** arm. Using the chi-square test, and the assumptions above, 121 participants in each group will give us 80% power to detect this difference with a type I error rate of 5%.

Given retention rates from our earlier studies, we expect attrition rates to be approximately 20% over the 6 month study period. Therefore, we anticipate needing to enroll 300 participants at baseline in order to have 242 active participants at 6 months.

Statistical Analyses:

We will first summarize all baseline measures globally and by treatment group. Categorical variables will be presented by frequencies and percentages within each of the possible categories and quantitative variables will be presented by means and standard deviations. Then, generalized linear modeling and mixed modeling will be applied to hypothesis testing for the primary and secondary aims (see below). In addition, for the exploratory purpose, we will evaluate potential covariates including smoking history and demographic, psychological, and sociocultural factors that may contribute to smoking abstinence. Interactions between intervention and these factors will also be investigated (i.e., moderation). All analyses will be conducted using SAS 9.2.^{[82](#)}

Primary Aim/Hypotheses:

1. To test the effectiveness of the **I-ANBL** compared to the **I-FV** on smoking cessation among tribal college smokers.

Hypothesis 1: At 6 months, participants in the **I-ANBL** group will show higher 7-day point prevalence abstinence rates than those in the **I-FV** group.

We will compare the salivary cotinine verified prevalence abstinence rates at 6 months between the two groups using logistic regression. For our primary comparison, we will conduct per-protocol analyses on (a) only the participants who complete the study, as well as intent-to-treat analyses on (b) all subjects by imputing the dropouts as smokers and (c) all subjects by using the Markov Chain Monte Carlo (MCMC) imputation technique. In (c), the missing data related to attrition can be reasonably assumed to be missing due to known characteristics of our database (i.e., missing at random). We will create a large number of (e.g., 200) complete datasets via expectation-maximization algorithm as prior estimates for the MCMC procedure;^{[83](#)} and then combine the analysis outcomes from each complete dataset to make valid statistical inferences.^{[84](#)} To evaluate secondary endpoint, we will compare the salivary cotinine verified prevalence abstinence rates between the groups at Week 12 (end of pharmacotherapy). Finally, as we have no preliminary estimates of relapse based upon timeline follow-back, we will conduct explanatory, failure analyses to compare the time to relapse between the groups. We will calculate failure function (cumulative probability of smoking cessation as a function of time) and fit Cox regression models to the 6-month self-report data on smoking status.

Secondary Aims/Hypotheses:

1. To test the effects of the intervention on intermediate smoking variables including number of cigarettes smoked and number of quit attempts at 6 months following randomization.

Hypothesis 1A: At 6 months following randomization, among those who continue to smoke, participants in the

I-ANBL group will show a greater reduction in the number of cigarettes smoked than participants in the **I-FV** group. Mixed models for repeated measures will be used to examine the change in the number of cigarettes smoked over the 6-month study period. To evaluate group differences of reduced cigarette numbers, the models will examine the main effects of time, treatment, and the number of cigarettes smoked at baseline and their interactions. Estimated means at 6 months, which are adjusted for the baseline cigarette numbers, will be reported and compared between the groups.

Hypothesis 1B: Smokers receiving I-ANBL will make greater number of serious quit attempts than smokers receiving I-FV. We will compare the number of quit attempts between the two groups using Poisson regression for count data. In the Secondary Aim 1 analyses, the dropouts will be handled by multiple imputation as described in Primary Aim.

2. To compare differences between **I-ANBL** and **I-FV** in adherence rates to program participation at 6 months following randomization.

Hypothesis 2: At 6 months following randomization, participants in the I-ANBL group will have significantly higher adherence rates than smokers in the **I-FV** group.

We will summarize and compare the measures of program exposure and dose between the groups by descriptive statistics and the *t*-test or chi-square test. Then, we will examine group differences in adherence rates by modeling the binary outcome (dropouts vs. completers) with logistic regression.

Data Management: Survey data will be entered into the REDCap system through our website directly by participants or, in the case of the initial interview, the facilitator while s/he is asking the questions. REDCap is an internet-based survey program that allows de-identified and encrypted data to be collected directly on a site. We have used this program in other studies and our Human Subjects Committee has determined that it is a safe and effective way to collect data remotely. It also allows the creation of separate databases for contact information so that we can maintain a numeric study-specific participant number as the only link between the study database and participant contact information. Data management activities will include conversion into proper format for data analysis and recoding. All data management activities will be supervised by Dr. Nazir.

Cost-effectiveness analysis: The purpose of our cost-effectiveness analysis is to establish the cost-effectiveness of the I-ANBL program relative to healthy heart diet intervention. While our cost analytic

framework follows the guidelines adopted by the CDC, we will assess costs from the service provider perspective rather than the recommended societal perspective. Given that there is widespread agreement that

the cessation of smoking behavior confers important societal benefits valued far in excess of the costs needed

to produce them, the research expenses needed to fulfill the societal perspective would exceed the benefit of

that approach. Instead, variable costs for each study arm will be valued in the year during which they are incurred. Discounting is not required for the six month intervention period, and research costs (\$20 gift cards) will be excluded from analyses.

Program costs that will vary depend on the number of participants include, personnel time, internet charges, materials (brochures and other handouts), pharmacotherapy, and participant incentives. Research assistant time for session support will be documented using a time diary/log and valued at wage rates including benefits. Phone charges for local and long distance calls will be applied to the time for telephone-based counseling. Pharmacotherapy costs will be valued according to IHS medication costs inclusive of dispensing fees. For sensitivity analyses, we will vary pharmacotherapy costs according to prevailing retail rates (market value) using the average of no fewer than three price sources (local pharmacy as well as on-line pharmacy options). Mailing costs will be added. Items included as incentives will be valued at their retail prices.

Dissemination of Study Findings to the Community

At study conclusion, results will be presented to Tribal colleges and their tribal community. Historically, AIs were studied for the sake of scientific research and received no benefit from participation. As such, it is important and necessary to provide the community with an understanding of the benefits they have gained from participation. In this case, a basic summary of results, including the numbers of people who successfully quit smoking, the number of smokers who participated in the study, and a basic summary of our outcome and process evaluation will be presented. In addition, all educational materials developed will be publicly available. The CAB will play a crucial role in decisions regarding dissemination to the community. All publications and presentations will require pre-approval by the Tribal colleges prior to submission or presentation.

VI. Plan for Monitoring and Reporting Unanticipated Problems

Data and Safety Monitoring Plan.

The purpose of this data and safety monitoring plan is to ensure the safety of study participants and the validity of data in compliance with National Institutes of Health/National Center for Minority Health and Health

Disparities/National Cancer Institute (NIH/NCMHD/NCI) requirement of Data and Safety Monitoring for Clinical Research. This section outlines essential elements of Data Safety and Monitoring (DSM) plan for this clinical research.

Monitoring the Progress of Trials and Safety of Participants. This study poses minimal risk to the participants as it involves the use of five Food and Drug Administration approved

products, the transdermal nicotine patch (TNP), nicotine replacement gum, nicotine replacement lozenges, varenicline, and bupropion hydrochloride. The safety of these agents has been assessed in multiple clinical trials of both smokers and non-smokers. The monitoring of the progress of the trial and the safety of participants will be overseen by Dr. Greiner who is a practicing physician.

Plans for Assuring Compliance with Requirements Regarding the Reporting of Adverse Events (AE).

The pharmacotherapy that will be used in this study has been approved by the Food and Drug Administration for aid in smoking cessation treatment. The adverse events associated with the TNP are few and mild and include skin irritation at the patch site and mild increases in heart rate and blood pressure. Adverse events related to nicotine gum and lozenge use are generally few and mild and can include hiccups, sore mouth and jaw, indigestion, headache, nausea, and insomnia. Studies have shown that varenicline is well tolerated, with few and mild adverse effects. The most common varenicline-related adverse effect is nausea, which is reported to be mild to moderate. Varenicline use will be monitored by the patient's primary care physician. The most common adverse effects associated with bupropion are dry mouth and insomnia. Subjects may also rarely complain of confusion, anorexia, or dizziness. Bupropion is also associated with a 1/1000 risk of seizures at the dose that will be used in this study. Factors that may increase the risk of seizures include: a history of head trauma, seizures, CNS tumors, excessive use of alcohol or cocaine, withdrawal from alcohol or benzodiazepines, and use of certain other drugs, including antipsychotics, antidepressants, theophylline, and systemic steroids. All patients will be screened for risk factors for seizures prior to recommending use of bupropion. Bupropion will only be provided to participants who have received a prescription from their primary care physician.

Participants will be prompted to discuss any adverse effects with their primary care physician or, if they do not have a primary care provider, with Dr. Greiner or the on-site clinician who will work with Dr. Greiner. Both subjects and physicians will be given the study office phone number (24-hour coverage) to contact study staff and/or investigators to report adverse events.

Furthermore, KUMC will be specifically asking participants weekly about potential adverse events (via our web-based communication system). Any report of an urgent/emergent or unexpected medical encounter by a study participant would automatically trigger an inquiry by our study personnel to find out what happened, create an AE report and forward that to Dr. Greiner and the on-the-ground physician to review and decide whether the AE was study or study medication related and whether participant should be taken off pharmacotherapy or should be advised to stop participating in the study.

Because the anticipated level of risk involved with all possible pharmacotherapy use is low, adverse events will be recorded and reported at the completion of the study along with other study results. In addition, serious adverse events will be monitored and handled as described below:

Definition: Consistent with the definition by the FDA, a serious adverse event includes any event experienced by a study subject while on the study medication that:

- Is fatal
- Is life-threatening (subject was at risk of death from the event as it occurred)
- Is disabling or incapacitating
- Requires inpatient hospitalization or prolongs a current hospitalization
- Is a congenital anomaly in the offspring of a subject who received the study medication
- Required intervention to prevent permanent impairment or damage

Monitoring: Information about serious adverse events experienced by study subjects will be monitored by the following means:

- Report given by study subjects to study staff either in person or by telephone
- Report given to study staff by study subjects' family or friends either in person or by telephone
- Report by the subject's physician or other health care provider involved in their care
- Report from a hospital or other healthcare facility where the study subject(s) is being treated for the serious adverse event
- Other persons that may have knowledge of such serious adverse event.

Procedure: Upon receiving report of a serious adverse event:

- The study staff will page Dr. Greiner (at beeper 917-4468) as soon as possible
- The study staff will give the necessary information to Dr. Greiner
- Dr. Greiner will obtain other necessary information and complete the "MED WATCH" form for each serious adverse event
- Dr. Greiner will make a decision whether to stop the study medication temporarily or permanently and inform study staff of this decision
- Dr. Greiner will complete the Adverse Event Report and submit completed form to the Human Subjects Committee of the University of Kansas Medical Center with 24 hours of their knowledge of the serious adverse event
- Dr. Greiner will inform the manufacturer of the drug (GlaxoSmithKline or Pfizer) and fax a completed copy of the "MED WATCH" to the manufacturer and the FDA. This should be done within 24 hours of their knowledge of the serious adverse event.
- A copy of the completed "MED WATCH" form will be kept in the study file.

Suicide/Homicide Procedures

Serious neuropsychiatric symptoms have occurred in patients taking Chantix. These symptoms include changes in behavior, agitation, depressed mood, suicidal ideation, and attempted and completed suicide. While some patients may have experienced these types of symptoms and events as a result of nicotine withdrawal, some patients taking Chantix who experienced serious neuropsychiatric symptoms and events had not yet discontinued smoking. In most cases, neuropsychiatric symptoms developed during Chantix treatment, but in others, symptoms developed following withdrawal of Chantix therapy.

As a result, special caution must be taken if a participant reports an *increase in depressed mood, agitation, changes in behavior not typical for them, or **suicidal thoughts or action** since starting the study medication*. The suicide/homicide protocol will be instituted for all participants noting changes of this sort since starting Chantix.

The suicide/homicide protocol is as follows:

1. Ask participant to describe their symptoms in more detail.

“Tell me more about what you are experiencing.”

2. Assess the level of severity.

“In general, would you say these symptoms are mild, moderate or severe?”

3. Assess attribution of symptoms to the study medication.

“Do you believe these symptoms are caused by the study medication or another cause?”

4. Assess suicide/homicide risk

Ideation:

“Are you having any thoughts of harming yourself or someone else?”

“What are the thoughts?”

“How long have you been experiencing them?”

Intent/Plan:

“Do you plan?” or “Have you thought about how you would harm yourself or someone else?”

“What is your plan?” or “How would you do it?”

Means:

“Do you have the means to carry out your plan?” (e.g., access to pills, a gun, etc.)

History:

“Have you had these thoughts before?”

“What have you done when you’ve felt this way?”

“Have you ever attempted to harm yourself or someone else?”

If yes, when did this occur?

How many times has it occurred?

What did you do? (e.g., take pills, gun, cut)

Were you hospitalized?

Social Support:

“Who do you talk to when you’re feeling this way?”

“Are you currently in counseling or treatment?”

Course of Action

1. If a participant reports **any** suicidal/homicidal ideation, including passive ideation (e.g., thoughts of death, would be better off dead, doesn’t care about living, etc.) or active ideation (has intent to harm, a plan, and means) advise them to stop taking the medication immediately.
2. If the participant is exhibiting active suicidal or homicidal ideation and DOES intend to harm him or herself or someone else:
 - a. Each local mental health center office provides 24 hour a day telephonic crisis response for any citizen in crisis. After discussing the person's problems on the phone the mental health professional (MHP) will decide whether a face to face evaluation is needed.
 - b. Where full time dedicated MHP teams exist, emergency crisis services are available to all persons for both telephone crisis support and face to face evaluations, where clinically indicated, on a 24/7 basis. In offices without dedicated full time crisis teams, clinicians are on call to respond to emergency requests for evaluation and dispositions only for WMMHC clients.
 - c. When a person is judged not to be in an emergency situation, as defined in Montana statute, the person may be given an emergency appointment at the local center for the next day, or referred to a local hospital for voluntary psychiatric admission, or linked with other community resources as appropriate.
 - d. If the individual has a primary therapist, who is not affiliated with the mental health center, that primary therapist will be contacted as soon as practical by the MHP.

- e. Stay with the participant until the crisis worker is able to intervene.
3. If the participant is exhibiting passive suicidal or homicidal ideation and does NOT intend to harm him or herself, the counselor should provide the participant with the **Mental Health Resource Card** and the **Crisis Referral List**. The counselor should also encourage the participant to seek support from friends, family, and possibly mental health resources.
4. If there is no suicide risk but the participant reports neuropsychiatric symptoms (increase in depression, change in mood, agitation, etc.) that are more than mild and that they attribute to the study medication, advise them to stop taking the medication immediately.
5. Regardless of the level of threat, a detailed case note must be made on the Adverse Event Report Log and Drs. Choi and Greiner must be contacted immediately. *Please note: **If a participant is actively suicidal, the first priority is to ensure their safety. Drs. Choi and Greiner should be contacted after the Crisis Worker has intervened.***

Plans for Assuring that any Action Resulting in Temporary or Permanent Suspension of the Research is Reported to the NCI Program Director Responsible for the Grant. Clinical research is subject to annual review and recertification by the Human Subjects Committee of the University of Kansas Medical Center. Any action resulting in temporary or permanent suspension of the research by the Human Subjects Committee, the FDA, or other authorized governmental agencies, will be reported to the NCI program director responsible for the grant.

VII. Study Withdrawal/Discontinuation Procedures

Participants may withdraw from the study at any time with no penalty for any reason. We will utilize whatever information we have at the time of withdrawal. All confidential information related to the participant who decides to withdrawal will be kept locked.

VIII. Plan for Assuring Subjects' Privacy and Confidentiality

Dr. Choi will retain copies of the signed consent forms throughout the course of the study. Standard language in our consent form assures the participant of the confidential nature of our study. These standards are strictly adhered to and monitored by the University of Kansas Human Subject Committee. Assigning each participant a study number, numerically coding all data, and de-identifying all transcripts of focus group discussions will maintain confidentiality. A key linking ID numbers with and participants' names will be kept by Dr. Choi in a locked file cabinet. Only summaries of findings will be reported in any publications or presentations, with no identification of individuals, individual facilities, or individual tribes.

IX. Follow-Up

Participants will be asked to return for a follow up session at 6 months after their first initial group or individual meeting.

X. Record Retention

All physical records will be kept in locked filing cabinets in offices that are kept locked when unoccupied. Subject files will be kept in a secure area, with access only by designated staff members (PI and Co-Investigators). The KUMC Department of Preventive Medicine has a well-developed structure for data management. Working data is maintained on a single large file server. Inactive files are moved to archival storage under control of an automated system, itself controlled by a DBMS (Ingres) based request system that ensures that all data movement is appropriately logged and commented. The archival storage is hosted on the institutional mainframe computer, which also supports billing and registration. The use of the mainframe ensures several high level support functions for the archive system (e.g., storage in separate fire zones, regular copying of data to new media, and guaranteed availability).

Data security and access will be governed by standard procedures. All analyses are logged with respect to IRB authorization, accounting information, principal and secondary investigators, statistician, and data analyst involved in the analysis. In order to create a unified data management strategy, we will identify all subjects with a sequentially assigned subject number and subject initials. To ensure subject confidentiality, no names, social security numbers, hospital or clinic numbers will be included in the shared databases. Names, addresses, telephone numbers, and any other information needed for recruitment, study involvement, and tracking will be obtained and maintained locally by the project personnel. All computer files and systems will be password protected and accessible only by authorized personnel.

In accordance with KUMC's Research Institute, Inc.'s Research Records Retention Policy (2004), Research Records are to be retained by the University of Kansas Medical Center (KUMC) for a period of six (6) years after the submission of the final report and close-out procedures on the research project for which the Research Records were prepared, unless a longer retention period is specified by the sponsor, funding source, or regulation. All research records and files related to this study will be destroyed 6 years after the completion of this study.