Protocol Title: Incentivizing behavior: promoting more physical activity in American Indian youth

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SPECIFIC AIMS

Half of adolescents in the United States fail to reach recommended levels of physical activity and nearly a third are overweight, elevating cardiometabolic risk early in life and setting the stage for adult disease. American Indians have the highest prevalence of type 2 diabetes in the United States, an elevated risk that is evident even in childhood. Thus, effective interventions are needed to reduce the lifetime medical and socioeconomic burdens of diabetes and related diseases. Through our prior clinical and research partnerships with American Indians in Oklahoma, we have gained insight into the health concerns of American Indian youth and the importance of community and healthcare leaders in developing creative collaborative approaches that work towards solutions. Based on this expertise, we developed the proposed strategy to improve the health of sedentary, obese American Indian youth by providing incentives for increased physical activity.

The high-risk youth who will be enrolled in the proposed study live in a predominantly rural, low socioeconomic region of Oklahoma. They currently have access to several well-equipped fitness centers in the region, but these resources are underutilized. Although it is well-accepted that regular exercise can improve individual health and reduce the socioeconomic burden of diabetes, reducing barriers and effectively modifying behavior presents a significant challenge. Prior studies have shown that paying adults for desired behaviors and/or health outcomes can be effective, but the use of financial incentives to shape exercise behavior in adolescents has not been reported. We hypothesize that monetary incentives will encourage obese, insulin resistant American Indian youth to establish and maintain better exercise habits, ultimately resulting in better health. We propose to provide transportation for participants to the wellness centers and individually tailored instruction and oversight by fitness professionals so that the centers are accessible and appealing. The provision of monetary incentives is designed to reinforce the frequency and duration of exercise. Our strategy to accomplish these goals is outlined in the following Specific Aims:

Aim 1: To determine whether financial incentives will increase the frequency of exercise sessions performed by American Indian youth at a community fitness center. Obese, insulin resistant American Indian adolescents will be randomly assigned to one of two groups for a 16-week exercise program: Control ($4/session, up to 3 sessions/week, provided as compensation for time), or Incentive ($4, $10, and $16 for the first, second, and third session each week, respectively). All participants will be provided transportation to and from the fitness center and professional instruction and supervision for aerobic exercise training, but will differ only in the amount of money they are eligible to collect for their attendance. A secondary goal of this Aim is to assess the association between exercise frequency and changes in diabetes-related risk factors, including insulin sensitivity, body composition, and blood lipids.

Aim 2: To determine whether financial incentives will increase the duration of exercise performed by American Indian youth at a community fitness center. Participants who complete Aim 1 will be re-randomized to one of two groups for a second 16-week period of exercise: Control ($4/session, up to 3 sessions/week), or Incentive ($4, $7, or $10 for 20-, 40-, or 60- minute sessions, respectively, up to 3 sessions and $30/week). Transportation and professional supervision will remain the same as in Aim 1. A secondary goal is to assess the association between exercise duration and changes in diabetes-related risk factors.

Aim 3: To determine whether ongoing incentives are required for maintenance of fitness center utilization established with financial incentives. Participants who complete Aim 2 will enter a third 16-week exercise period with diminished monetary incentives. Each person will be re-randomized to one of two incentive structures: a) Ramp-down, with financial incentives diminishing to zero by 8 weeks, or b) Raffle, with monetary prizes awarded through a drawing in which chances of winning are dependent on frequency and duration of exercise. We hypothesize that exercise behavior will remain above zero even after financial incentives decline and that the Raffle approach will reinforce the best exercise behavior maintenance. Clinical diabetes risk outcomes will be measured as in Aims 1 and 2.

Aim 4: To measure the impact of physical activity and physical fitness on circulating biomarkers of metabolic disease risk. Normal weight American Indian youth with either low physical activity and fitness or high physical activity and fitness will be studied on a single occasion. Serum/plasma concentrations of lipids, amino acids, and related markers of inflammation, and oxidative and vascular stress will be compared among the normal weight participants and the overweight/obese youth enrolled in Aims 1-3.

This study will clarify how specific incentive structures can be used to promote exercise in a population of adolescents at exceptionally high risk for diabetes and cardiometabolic disease. The study will also provide needed insight on the volume of exercise needed to elicit changes in clinical outcomes. These results will be used to develop better lifestyle intervention strategies for American Indian youth.

RESEARCH STRATEGY: APPROACH

Design: Specific Aims 1-3 will follow a single prospective, randomized trial design, with 105 participants enrolled and 80-90 entering the exercise program (**Fig 1**). The individual Aims are distinguished by sequential study phases and varying incentive structures (**Fig 2 and 3**). Aim 4 is a cross-sectional comparison between overweight/obese participants entering the main trial and two groups of normal weight youth (up to 40 participants per group) with either low physical activity and fitness or high physical activity and fitness (up to 40 participants per group).

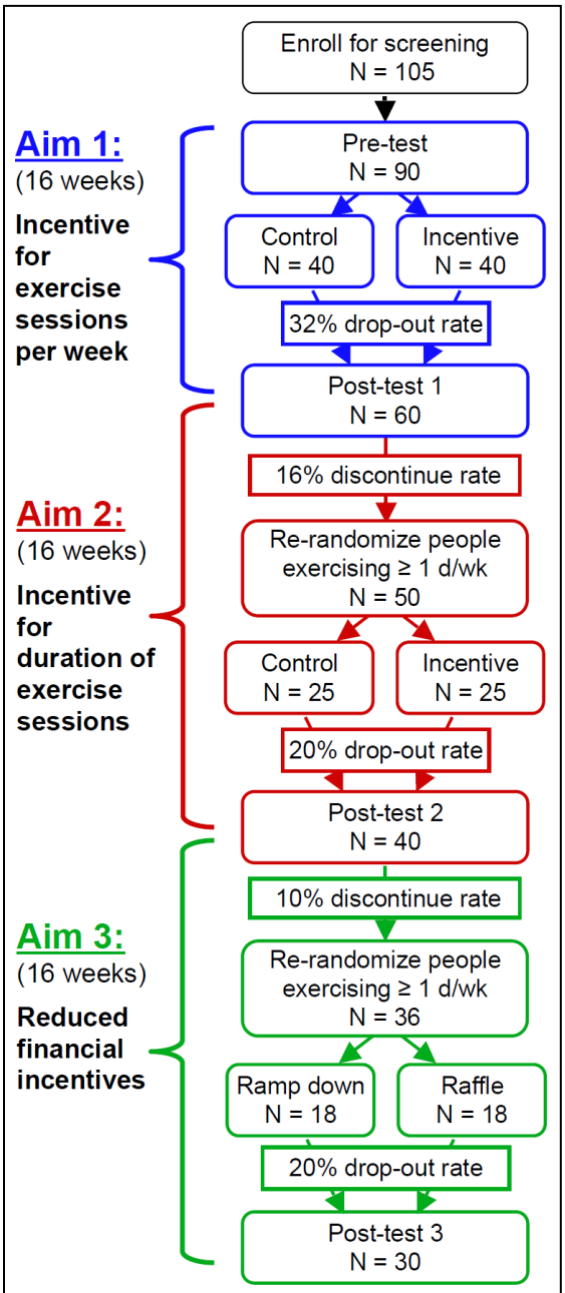

Fig 1. Projected protocol flow.

Participants: Male and female American Indian youth 11-21 years old will be recruited from the Choctaw Health Service Area of SE Oklahoma. For the primary exercise incentives study, the eligibility criteria include BMI ≥85th percentile for age- and sex-specific norms based on growth charts from the Centers for Disease Control, maturation level ≥Tanner Stage 2 for breasts (girls) or genitalia (boys), family history of T2D, and recent history of low physical activity. Low physical activity, defined as attaining <30 minutes of structured moderate-to-vigorous intensity exercise on ≤ 3 days/week over the preceding 3 months, will be confirmed through questionnaires and objective monitoring as described below. For both normal weight comparison groups in Aim 4, eligibility will include BMI greater than 20th and less than 85th percentile, maturation level ≥Tanner Stage 2 for breasts (girls) or genitalia (boys), and recent history of either a) low physical activity (same as the overweight/obese group) or, b) high physical activity (>30 minutes of structured moderate-to-vigorous intensity exercise on >3 days/week over the preceding 3 months. T2D family history will be recorded but will not be an inclusion criterion for the normal weight groups. Fitness level and physical activity will be determined through testing, described below. Additional enrollment and retention eligibility criteria are: lack of diabetes or other potentially confounding metabolic disorders, able to safely exercise, willingness to complete the testing and participation schedule, and not on medications known to impact the stated outcomes. A medical history and physical exam will be performed to assure suitability for the study during the initial screening.

Protocol: All overweight/obese participants will follow the same protocol. After an initial screening to ensure eligibility, a standard set of clinical outcome assessments will be performed at baseline (Pre-test), after completing 16-weeks of exercise training in Aim 1 (Post-test 1), again after completing the second 16-week exercise period in Aim 2 (Post-test 2), and once more after completing the 16-week exercise period in Aim 3 (Post test 3). Normal weight participants enrolled into Aim 4 will complete only the screening and baseline tests; they will not continue with the incentivized exercise program.

Screening: During this visit, informed written consent/ assent of participants and their parents will be obtained in accordance with IRB guidelines. A medical history and physical exam will be performed. Each child and a parent/guardian will be interviewed to educate them on their child's health status, the importance of physical activity as a component of a healthy lifestyle, and the potential improvements in clinical outcomes that may occur in response to increased exercise behavior. The interview will also be used to assess potential barriers to change. This may include, but is not limited to several identifiable personal and environmental concerns that could interfere with the child's ability to complete the study, such as family employment demands, income and education status, transportation and food availability, social structure, and competing

time demands. A comprehensive, individualized plan will be developed to reduce barriers. A motivation assessment questionnaire with established validity and reliability (62, 73, 91) and adapted for a rural community will be used to evaluate preferred types of exercise, social support, and perceptions of barriers to exercise by child and family. Community and environmental barriers to exercise will also be assessed. The Choctaw Nation of Oklahoma offers several social service programs designed to eliminate distress, including academic tutoring, mentoring, organized activities, housing assistance, nutrition classes, and counseling. Many of these services are located near the Wellness Centers. The interviewer will be responsible for linking the family to these services when appropriate and performing follow-up to address new and existing barriers. The goal of this effort is to insure that a decision by the child or family to discontinue the study is due to choice and not due to barriers that can be reasonably addressed.

Baseline pre-training testing: The baseline tests may be combined with the screening visit. Baseline tests will be comprised of measurements of daily physical activity, aerobic fitness, body composition, and insulin resistance. Daily physical activity will be objectively measured with a step-activity monitor worn for 7 days during waking hours. Participants will be asked to maintain their normal lifestyle patterns during this time. A registered dietitian will provide instruction on a healthy eating plan but specific weight loss goals or dietary monitoring will not be part of this study. Insulin resistance and other clinical outcomes will be assessed using fasting blood samples. Participants will report to the research center in the morning following an overnight fast. Body composition and exercise tests will be performed as described below.

Exercise training: The 16-week Aim 1 exercise training period will begin within two weeks after the Pre-test. Training sessions will be performed at one of the Wellness Centers described in Facilities, with potential for additional sites depending on needs and the availability of appropriate supervision. All participants already have free membership to the Wellness Centers as a benefit provided to Certificate Degree of Indian Blood (CDIB) cardholders. Free transportation will be arranged through a shuttle service already in place for medical visits. Fitness professionals at each center will provide instruction, supervision, and ongoing guidance to assure that exercise sessions are completed safely and effectively. Participants and their parent/guardian will be instructed that the exercise goal throughout the entire 48-week study is to achieve 60 min/day of moderate-to-vigorous physical activity (MVPA), consistent with current guidelines for children (13, 31, 90). MVPA is defined as continuous exercise that elicits a heart rate ≥ 70% of peak heart rate. Each participant will be able to choose the frequency of visits to the wellness center and the length of time engaged in MVPA, since the purpose of the study is to test the effect of incentives on exercise behavior. Several types of exercise can be selected, including walking, running, cycling, stair stepping, aerobic dance or other activities. Instructors will advise a gradual increase in exercise intensity and duration as tolerated over the first 2-3 weeks to allow for familiarization and safety. To promote healthy behavior within the community and foster social support, all participants will be invited to exercise with family members or friends if they choose and this will be recorded as a covariate. As in our previous studies, exercise intensity will be monitored by recording heart rate with a chest strap transmitter that outputs to a computer for quantification and data storage. These data will be used to document training sessions. To provide backup in the event of technical failure, training sessions will also be recorded in an exercise log by each participant and confirmed by fitness center staff. Exercise will be quantified by frequency (sessions per week), duration (length of sessions), and total volume (Metabolic Equivalent of Task-hours, MET-h, a measure of intensity relative to resting x activity time).

After completing Aim 1 and the associated post-test, all participants who completed an average of ≥ 1 exercise session per week will be eligible to continue on to Aim 2. The only difference between Aims 1 and 2 will be the financial incentive scheme; the overall exercise goals, and provision of transportation and professional oversight will remain the same. Similarly, after completing Aim 2 and the associated post-test, all participants who have averaged ≥ 1 exercise session per week in Aim 2 will be eligible to continue on to Aim 3. No changes will be made to the exercise goals or availability of transportation and facilities in Aim 3.

To allow for potential schedule conflicts and missed sessions (e.g., illness, travel) participants will be allowed to “catch-up” by performing up to 3 extra sessions within the 3 weeks following a week with less than 3 sessions. Thus, if an entire week is missed due to illness, 12 sessions for payment can be completed over the next 3 weeks instead of the targeted 9 sessions. Additionally, participants will not be discouraged from performing more than the targeted exercise volume of 3 days per week of 60 minutes per session. Exercise beyond this target that is performed at school, at home or at the Wellness Centers is acceptable, since the goal of this program is to foster increased physical activity. Participants will be instructed to include such extra

physical activity in their exercise log book, though they will not receive payment for days or time beyond the structured incentive program. This information will be used as part of the data analysis plan if applicable.

Post-training testing: After each of the 16-week exercise phases in Aims 1, 2, and 3, the clinical outcome tests performed at the baseline will be repeated. Staff that supervise exercise sessions will not be blinded to group assignment, but most other staff, including nurses and chemistry lab staff, will not know group assignments, so the potential for bias is expected to be low. The fasting blood sample will be acquired 2 days (38-48 hours) after the last exercise session in order to assess exercise adaptations that are distinct from the residual effects of the most recent training session. The exercise fitness and body composition tests will also be repeated at the end of each study phase.

Group assignment: Within each Aim, participants will be assigned to one of two groups using a randomized stratified block design that was selected to reduce the potential for baseline variability among the groups. Participants will be assigned to blocks of 2 (duos) matched for age and sex. A participant who is not yet matched on the two factors will determine the age and sex for a newly established duo. The next participant to meet those matching criteria will be assigned to that duo. Each duo will have one participant in each of the intervention groups, but the group to which each participant in a block is assigned will be pre-determined by a unique random permutation.

Incentive programs

Overview and rationale: Each participant will receive $50 for completing the initial screening visit and baseline set of clinical and fitness tests. Normal weight participants in Aim 4 will stop after completing the baseline tests. Overweight/obese participants who continue into the exercise program will also receive and $50 each time they complete the end-of-phase set of clinical and fitness tests (3 Post-tests after each 16-week study phase). These payments are similar to amounts used in our recent and ongoing studies of children that have similar procedures and time requirements. The payment schedules for exercise sessions are detailed in each of the separate Aims sections below. We set the payment levels for Aims 1 and 2 based on our experience with exercise studies for adolescents. Payments were selected to be commensurate with the time commitment of participants, as well as the need to create a distinctly higher payment in the incentivized groups so as to elicit the targeted high adherence. The total time for testing and exercise sessions per participant is ~164 hours over ~50 weeks, not including transportation time to and from the participant's home or school and the wellness and testing sites. Depending on group assignment, the range of total compensation to participants who complete all assigned study visits will be $716-1,292, or ~$4.40-7.90 per hour of involvement. We deemed this to be an appropriate compensation/ incentive without inducing undue influence. Payments for screening and baseline test will be arranged at the time of completion using a reloadable debit card provided at no charge to the participants. Thereafter, payments for completed exercise training sessions and Post-exercise tests will be provided every 2 weeks for as long as the participant remains in the study.

Aim 1: This aim will test the hypothesis that the frequency of exercise sessions at the wellness center will vary with the amount of money offered for the number of sessions per week. Participants will be assigned to one of two groups that only differ in the payments for completing their exercise sessions. For both groups, payment will be provided for the number of sessions performed, up to 3 per week. As shown in **Fig 2**, the Control group can earn up to $12 per week at a flat rate of $4 per session, while those in the Incentive group can earn up to $30 per week through an incentive structure meant to encourage exercise on 3 days per week. Qualifying exercise sessions for both groups must be ≥ 20 minutes/session of MVPA during the first 3 weeks, increasing to ≥ 30 minutes/ session of MVPA in weeks 4-16. To allow for rest breaks, the activity time can be accumulated rather than continuous. The plan for recording sessions and making up missed sessions is outlined in the Exercise Training section. By completing all of the targeted 48 exercise sessions participants can earn a maximum of $192 (Control) or $480 (Incentive) for exercise in this Aim.

Aim 1 payments, exercise sessions/week:

	Session of the week			
Group	Day 1	Day 2	Day 3	Max.
Control	$4	$4	$4	$12
Incentive	$4	$10	$16	$30

Aim 2 payments, exercise time/session:

	Time per session			
Group	20 min	40 min	60 min	Max.
Control	$4	$4	$4	$12
Incentive	$4	$7	$10	$30

Fig 2. Aims 1 & 2 incentive structures. Values are payments per visit and weekly maximum.

Aim 2: This aim will test the hypothesis that exercise time per visit will vary with the amount of money offered for the length of exercise sessions. In this aim, as in Aim 1, the Control group will earn $4 per session for up to 3 sessions per week. The Incentive group can earn up to $30/week, with a payment structure based on the length of time for each exercise session (**Fig 2**). The incentive is meant to encourage at least 60 minutes of MVPA per exercise session, consistent with the daily activity recommendations for youth. As in Aim 1, this study phase is 16 weeks so completion of all 48 targeted exercise sessions will result in payments of $192 (Control) or $480 (Incentive).

Aim 3: This aim will determine if exercise behavior developed during the preceding 32 weeks will continue when payments for exercise are diminished. Participants will be randomized to either the Ramp-down or Raffle group. Maximum payments for the Ramp-down group will begin at $20/week, through a payment structure that incentivizes exercise time, as in Aim 2, with a bonus for completing 3 sessions in a week (**Fig 3**). The weekly payments will be decreased over 8 weeks, reaching $0 for weeks 9-16. The Raffle group will earn chances to win prize money based on the number of fitness center exercise sessions and time spent exercising each week. The number of raffle entries earned for each session will vary from 1-16 per participant each week (**Fig 3**). Random drawings will be conducted to determine winners, with the total value of the weekly prize pool set to ~$7 per person. All participants will continue to receive the same transportation and Wellness Center access as before. Total potential payment for exercise in Aim 3 will be ~$112 per participant, though the actual amount for Raffle group members will vary according to chance.

Aim 3 Ramp-down payments:

	Time per session			3d/wk	
Week	20 min	40 min	60 min	Bonus	Max.
1	$2	$4	$6	$2	$20
2	$2	$4	$6	$2	$20
3	$2	$4	$5	$2	$17
4	$2	$4	$4	$2	$14
5	$1	$2	$4	$2	$14
6	$1	$2	$3	$1	$10
7	$1	$1	$3	$1	$10
8	$1	$1	$2	$1	$7

Aim 3 Raffle chances earned:

Exercise time per session	Session of the week			
	Day 1	Day 2	Day 3	Max.
20 min	1	2	3	6
40 min	2	3	5	10
60 min	4	5	7	16

Fig 3. Aim 3 incentive schemes. The Ramp-down bonus is for completing 3 sessions/week. Max. = total payment or raffle chances per week.

Clinical outcome tests

Insulin sensitivity: Fasting insulin sensitivity will be assessed by Homeostasis Model of Assessment - Insulin Resistance (HOMA-IR), calculated as: [fasting insulin (μIU/ml) x fasting glucose (mg/dl)/405].

Anthropometry and blood pressure: Height, body mass, and waist and hip circumference will be measured by trained nurses. As regularly performed by our lab, total body and regional fat and lean tissue will be measured using bioelectrical impedance analysis at each of the pre- and post-training visits. Blood pressure will be measured in duplicate after the child has rested quietly for 15 minutes using an appropriately sized arm cuff.

Fitness testing: Bicycle ergometer tests with increasing workloads will be used to measure maximal aerobic work output, peak rate of oxygen consumption (VO_2peak) and heart rate, and the workload corresponding to a heart rate of 170 beats/min (48, 77). Submaximal stages will be used to establish relationships among heart rate and power and used to assess work economy. Continuous measurements of expired gases will be performed with a facemask and metabolic measurement cart and heart rate with Polar heart rate monitors. For normal weight participants, the cut point for fitness level (low versus high) will be a VO_2peak of 46 ml/kg/min for boys and 37 ml/kg/min for girls. This threshold was identified as a marker of elevated metabolic risk, based on a composite of standard clinical outcomes such as blood pressure, glucose, lipids, and waist circumference, in a cohort of more than 2,000 adolescents (age ~15 y), who performed a standard bicycle fitness test (4).

Physical activity assessment: Free-living daily ambulatory activity will be measured with accelerometers worn on the waist (Fitbit Zip, Fitbit Inc.) throughout the day, recording data each minute for 7 days. Data analysis includes total step count and activity patterns based on step rates. We have recently completed validation and reliability assessments of these monitors in our laboratory have found very high levels of agreement with other waist or ankle-worn accelerometers.

Plasma/serum analysis: In addition to measurements of glucose and insulin performed to measure insulin resistance, blood will be collected for measurement of lipids, inflammatory and related disease risk markers. All planned assays are established on campus or in our laboratory. Lipid analyses include total-, HDL- and LDL-cholesterol and non-esterified fatty acids (colorimetric assay, Wako Chemicals, Richmond, VA). Pro-inflammatory biomarkers associated with obesity and insulin resistance include oxidized LDL (oxLDL) and HDL (oxHDL), high-sensitivity C-reactive protein, myeloperoxidase, high-molecular weight adiponectin, visfatin, and the soluble vascular-derived molecules, intercellular cell adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), measured with ELISAs from Phoenix Pharmaceuticals, R&D Systems and Millipore. Additionally, we will measure the plasma concentration of a panel of amino acids and their metabolites (particularly isoleucine, leucine, valine, and adiptic acid), and a panel of fatty acyl CoA's, that have been reported to be increased in children and adults with diabetes, and have been shown to predict the future onset of diabetes (2, 3, 8, 16, 39, 57, 64, 74, 75, 83, 101, 104, 105). Hemoglobin A1c will be measured to assess recent history of glycemic regulation and diabetes risk (Choctaw Nation Health Clinic). Blood collection, sample analysis and destruction of unused samples will adhere to NIH, IRB and Choctaw Nation of Oklahoma guidelines.

Data analyses: Since group assignments will be balanced for age and sex, the groups are expected to be similar at baseline. Additional comparisons will be performed to identify demographic or other variables on which the groups might differ (e.g., weight loss) that could affect the primary outcomes. Subsequent analyses will adjust for these potentially confounding variables. Regression models, which adjust for modifier (or confounding) variables identified in initial data exploration, will compare between-group differences in the primary outcomes. Since we anticipate that the number of fitness center visits, which is the primary outcome in Aim 1, will follow a Poisson distribution typical of counts, we will explore a multivariable Poisson regression model to analyze that aim. To assess Aim 2, a more conventional regression model will analyze the primary outcome, which is the total time that participants engage in exercise. The effects of exercise training on secondary outcomes will be analyzed similarly, using multiple linear regression. Analysis of Aim 3 will also utilize multivariate modeling to determine which factors, including exercise group assignment, best explain the change in exercise volume and clinical outcomes over the final phase of the study. Residuals generated from regression models will be inspected for normality and data will be log-transformed or subjected to non-parametric testing as appropriate. Aim 4 is a cross-sectional study design so the main effects of physical activity (high versus low), fitness (high versus low) and body size (normal weight versus overweight/obese) on biomarkers of metabolic disease risk will be initially determined using an analysis of variance approach, with Bonferroni tests to make pairwise comparisons between groups. A multivariate modeling approach, similar to that used in Aims 1-3, will be used to identify the best sets of predictor variables for specific biomarkers. A P value <0.05 will be considered statistically significant.

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