Study Protocol For A Cluster Randomized Trial of A School, Family and Community Intervention For Preventing Drug Misuse Among Older Adolescents in the Cherokee Nation

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Abstract

Background: The national opioid crisis has disproportionately burdened rural White populations and American Indian/Alaska Native (AI/AN) populations. Therefore, Cherokee Nation and Emory University public health scientists have designed an opioid prevention trial to be conducted in rural communities in the Cherokee Nation (northeast Oklahoma) with AI and other (mostly White) adolescents and young adults. Our goal is to implement and evaluate a theory-based, integrated multi-level community intervention designed to prevent the onset and escalation of opioid and other drug misuse. Two distinct intervention approaches—community organizing as implemented in our established Communities Mobilizing for Change and Action (CMCA) intervention protocol, and universal school-based brief intervention and referral, as implemented in our established CONNECT intervention protocol—will be integrated with skill-based training for adults to strengthen social support for youth and strategic media. Further, we will test systems for sustained implementation within existing organizational structures of the Cherokee Nation and local schools and communities. This study protocol describes the cluster randomized trial, designed to measure implementation and evaluate effectiveness on primary and secondary outcomes.

Methods: Using a cluster randomized controlled design and constrained randomization, this trial will allocate 20 high schools and surrounding communities to either an intervention or delayed-intervention comparison condition. With a proposed sample of 20 high schools, all enrolled 10th grade students in fall 2021 will be eligible for participation. During the trial, we will: (1) implement interventions through the Cherokee Nation, and measure implementation processes and fidelity; (2) measure opioid and other drug use and secondary outcomes every six months among a cohort of high school students followed over three years through their transition out of high school; (3) test via a cluster randomized trial the effect of the integrated CMCA-CONNECT intervention; and (4) analyze implementation costs.

Discussion: This trial will expand upon previous research advancing the scientific evidence regarding prevention of opioid and other drug misuse during the critical developmental period of late adolescent transition to young adulthood among a sample of American Indian and other youth living within the Cherokee Nation reservation.

Trial registration: ClinicalTrials.gov, NCT04839978. Registered April 9, 2021, <https://clinicaltrials.gov/ct2/show/NCT04839978>

Contributions To The Literature

- Rural Whites and American Indian/Alaska Native (AI/AN) populations are two subgroups that have been hit hard by the opioid crisis, as well as experience persistent disparities related to alcohol problems and suicide risk. Early onset of alcohol and other drug use during the adolescent years is a risk for transition to substance use disorder in adulthood.

- This study will be the first to test a theory-driven and community-engaged implementation of an integrated school, family and community drug preventive intervention to target opioid and other drug misuse among older adolescents in the context of rural, American Indian, and multiracial communities within the boundaries of a tribal reservation.
- Findings will contribute to gaps in the implementation literature regarding implementation processes and effectiveness of school, family and community prevention strategies in under-resourced and under-served rural and tribal communities.

Background

Increased rates of drug and opioid involved overdose deaths, along with alcohol-related mortality and suicide, have contributed to an unprecedented rise in midlife mortality—compellingly labeled as “deaths of despair” [1, 2]. Significant and widening disparities exist for subgroups of the population by race/ethnicity, socioeconomic status, and geographic area—disparities driven by adverse economic trends, socioeconomic inequality, and vulnerabilities due to historical trauma, discrimination and lack of resources [2]. Rural Whites and American Indian/Alaska Native (AI/AN) populations are two subgroups hit hard by the opioid crisis, and have also experienced persistent disparities related to alcohol and suicide risk [2–4].

The COVID-19 pandemic heightened concern for risk of mental health and substance use problems [5–7]. Indeed provisional data indicate an alarming 27% increase of drug overdose deaths from September 2019 to September 2020 rising to rates higher than during the previous height of the opioid epidemic in 2017 [8]. Survey data from June 2020 indicate that nearly half of adults reported at least one adverse mental or behavioral health symptom, with the highest levels among young adults aged 18–24 years (75%) and those who held less than a high school diploma (66%) [9]. Young adults reported significant increases in mental health and substance use symptoms during COVID-19 [10].

Primary prevention, by addressing risk and protective factors related to the onset and sequence of mental health symptoms and drug use, is key to reversing the alarming trends and disparities. Early onset of drug use during the adolescent years is a risk factor for faster transition to substance use disorder during adolescence and into adulthood. Adolescents aged 12 to 17 who reported initiation of cannabis or prescription misuse during the past year were nearly twice as likely to have a substance use disorder (SUD) than young adults aged 18 to 25 who initiated within the past year [11]. Alcohol and cigarette use preceding initiation of marijuana use remains the most prevalent sequence of drug use onset among youth, but opioid misuse is playing a more prominent role in the development of SUDs among younger generations [12]. Adolescents who engage in simultaneous co-ingestion of opioids and other drugs have greater odds at age 35 of alcohol use disorder, cannabis use disorder, other drug use disorder and any substance use disorder, relative to those with no history of non-medical opioid use during adolescence [13].

The current trial was funded through the NIH Helping to End Addiction Long-term (HEAL) Initiative. The National Institute on Drug Abuse (NIDA) is supporting a series of studies to develop and test effective strategies to prevent opioid misuse and opioid use disorder among vulnerable populations, including older adolescents and young adults and AI/AN communities. NIDA has also funded a coordinating center to facilitate data harmonization, implementation science, cost effectiveness research, and dissemination of study findings.

Our trial is unique among the NIDA-funded opioid prevention studies with its focus on universal primary prevention for rural older adolescents living in or near the boundaries of the Cherokee Nation reservation, a 6950 square mile area within 14 counties of northeast Oklahoma. Within the reservation area fixed by treaty in 1866, the Cherokee Nation currently shares jurisdictional authority with the State of Oklahoma and county and municipal governments. Cherokee Nation is the largest federally recognized American Indian tribe with 369,295 registered tribal members. During 2014–2016, within the 14-county region, the age-adjusted rate of overdose death involving opioids ranged from 13 to 36 per 100,000 [14], the lower end of the range being higher than in Oklahoma (11.6) and similar to the U.S. average (13.3) [15]. Oklahoma has had one of the highest rates of opioid overdose mortality [3], and provisional data indicate that drug overdose deaths rose by 16% from September 2019 to September 2020 [8].

The preventive intervention will be implemented through Cherokee Nation Behavioral Health and builds upon the strengths and services provided by Cherokee Nation Health Services, which is the largest tribally-operated health care system in the U.S. [16]. Cherokee Nation Behavioral Health provides prevention, treatment, and recovery services [17]. Prevention activities include public education, social norm campaigns, training to schools and other community organizations, and individual, family, and group counseling. Treatment services include medically-assisted treatment, assistance for inpatient treatment, and wraparound care management for clients and their families. In 2013, Cherokee Nation Behavioral Health started the Helping Everyone Reach Out (HERO) Project. The HERO Project is a comprehensive strategy to improve outcomes for Cherokee (and other American Indian) children and families within the Cherokee Nation reservation by providing a spectrum of community-based services and support for children and youth with or at risk for mental health or other challenges. Cherokee Nation Behavioral Health has emphasized children and youth services and public health approaches to reach an underserved population with high rates of trauma, setting the stage for partnerships with academic partners to meet challenges with community-driven approaches.

In a previous NIH-funded prevention trial in the Cherokee Nation, we found that an alcohol-focused school- and community-based preventive intervention reduced alcohol use among adolescents, but also had beneficial spillover effects that reduced other drug use, including prescription drug misuse [18, 19]. Other prevention trials have also found that involving multiple community systems is effective for the prevention of drug use among adolescents and young adults [20, 21]. Interventions to prevent initiation and progression of alcohol, marijuana, and opioid misuse among rural adolescents need to address barriers to accessing health and social services, facilitators of access to harmful drugs, family and community cohesion, and educational and economic opportunities [2, 22, 23]. Given the multi-level and

multi-system determinants of substance misuse, we have designed a multi-level intervention with delivery at the school and community levels.

Contribution of this trial

This study will be the first to test a theory-driven and community-engaged implementation of an integrated school, family and community drug preventive intervention to target opioid and other drug misuse among older adolescents in the context of rural, American Indian, and multiracial communities within the boundaries of a tribal reservation. Findings will contribute to gaps in the implementation literature regarding implementation processes and effectiveness of school and community prevention strategies in under-resourced and under-served rural and tribal communities.

Objectives and aims

The trial will achieve the following aims: (1) implement school, family and community-level interventions through existing structures of Cherokee Nation Behavioral Health and Oklahoma public schools, and measure implementation processes and fidelity at the individual, school, and community levels, (2) measure primary drug use and secondary outcomes at the individual level, (3) test the effect of the integrated community (CMCA) and school and family (CONNECT) intervention, and (4) analyze implementation costs.

Methods

Trial design

The study design is a cluster randomized trial (CRT) with one baseline survey and six follow-up surveys (Fig. 1). The intervention condition involves exposure to three years of an integrated multi-level intervention within the school and community. The control condition communities will be offered the project intervention materials, resources and trainings after follow-up evaluation has been completed. Baseline assessment will take place among a cohort of youth during the fall semester of 10th grade before intervention initiation. Intervention activities will begin during the cohort's 10th grade year, and will continue regardless of school status and for six months following on-time graduation. Students who are suspended, expelled or drop out of high school and remain within the community will continue to be tracked for follow-up surveys. Follow-up surveys will be conducted every six months over a three-year period measuring changes in proximal and distal outcomes as the intervention is initiated, ramps up, and becomes routine. The final follow-up survey will be conducted six months after on-time graduation, allowing assessment of changes in drug use outcomes during the important transition from high school to young adulthood.

Human subjects' approval was received from the Cherokee Nation IRB, which is serving as the single IRB for this multi-site trial involving Cherokee Nation Behavioral Health and Emory University. All data collected will be de-identified and stored on secure servers accessible only to members of the research

team. Any adverse events or protocol modifications will be tracked and, when indicated, reported in a timely manner to the institutional review board and funding agency.

Study setting, participants, and recruitment

The target population is students attending high schools in small rural towns in the 14 counties that partially or fully fall within the Cherokee Nation reservation. Figure 2 displays a planned flow chart for the study. Inclusion criteria for high schools include: (1) counties that partially or fully fall within the Cherokee Nation reservation, (2) town population of 3,000 or fewer, and (3) class size between 30 to 100 students. Exclusion criteria include: (1) metropolitan and micropolitan cores (Census Bureau Rural-Urban Commuting Area codes 1 and 4), and (2) existence of an established community drug prevention coalition. Based on the study inclusion and exclusion criteria, 28 of 60 schools met eligibility criteria. Eligible school/community units were selected for the first phase of recruitment based on geographic separation to reduce spillover risks of the community-level intervention. Twenty-four schools were invited to a recruitment meeting, 22 responded and attended a Zoom meeting with the project team. Twenty of the 22 agreed to participate in the study.

All 10th grade students enrolled in the participating high schools during the fall 2021 semester will be eligible to participate in the study. Based on historical records from the 20 schools, we will recruit approximately 1,000 students. Participating schools will either provide the researchers with a list of the most current home addresses for all students in the grade cohort in the participating high schools or be provided with postage paid consent letters to mail directly from school. Parent/guardian consent letters describe the study and provide a toll-free telephone number that parents/guardians can call with questions or concerns. Home visits will be made when requested or if the parent is unavailable via telephone. Parents who refuse permission for their child to participate will be asked to respond by returning an addressed postage-paid postcard or by calling Cherokee Nation Behavioral Health or Emory University using toll-free telephone numbers. Also, each student will be given an assent form and opportunity to decide not to participate or withdraw their participation at any time.

Constrained randomization

Following recruitment of 20 school-based clusters conducted by the PIs (KAK, TKK, JRS) and project manager (BJL), clusters will be allocated to either the intervention condition or delayed-intervention control condition using constrained randomization by the project statistician (MDL). Constrained randomization helps to ensure balanced cluster sizes as well as similar levels of risk between the intervention and control at baseline [24]. Constrained randomization begins by enumerating all possible randomization schemes (184,756 for 20 clusters with 10 conditions per cluster). Possible randomization schemes are then removed that do not achieve a priori balance conditions, while leaving enough candidate randomization schemes to maintain randomness. Existing guidelines indicate at least 1,000 candidate randomization schemes are sufficient for our study design [25, 26]. Finally, one of these randomization schemes is chosen at random. We constrained possible randomization schemes based on balance criteria for both high school and community characteristics (Table 1), resulting in 1,226 possible

randomization schemes of which one was randomly selected. Following randomization, participating schools will be informed as to their status as intervention or delayed-intervention control schools.

Table 1
Variables included in constrained randomization.

Characteristic	Balance for Constrained Randomization	Source
High School		
% American Indian	Within 5 percentage points	National Center for Education Statistics[27]
Absenteeism rate	Within 5 percentage points	Oklahoma School Report Cards[28]
% Free/reduced price lunch	Within 5 percentage points	National Center for Education Statistics[27]
Rate of substance use incidents per 100 students	Within 0.5 incidents per 100 students	Oklahoma Department of Education Annual Incident and Suspension Report[29]
Four-year graduation rate	Within 5 percentage points	Oklahoma School Report Cards[28]
Class size	Within 5 students or 10%	National Center for Education Statistics[27]
Community		
Medical marijuana dispensary	No more than 1 discrepant community across conditions	OMMA Dispensary List[30]
City police	No more than 1 discrepant community across condition	Google search
Mental health counselors	Mean number per condition within 1	OK State Board of Behavioral Health-LPC License Search[31]

Preventive interventions

We will implement an integrated community intervention that efficiently combines components from evidence-based strategies at the individual, social network, and community levels, with innovations designed to strengthen and enhance effects. The multilevel intervention is designed to reduce “demand” for and “supply” of drugs. Demand reduction strategies include enhancing social connections and support, building self-efficacy to avoid drugs, and supporting no-use norms. Supply reduction strategies include reducing access to drugs and supporting community norms around protecting youth from alcohol and other drugs.

CONNECT. The CONNECT school-based intervention will be administered by the youth services branch of Cherokee Nation Behavioral Health and primarily focus on demand reduction by strengthening self-efficacy, drug-free norms, and social connections and support. Two to three Bachelor's-level social workers (or closely related degree) will be hired to serve as CONNECT coaches in the 10 intervention schools. Their direct supervisor will be a Cherokee Nation Behavioral Health licensed clinical social worker who is trained and experienced using motivational interviewing (MI), specifically with American Indian youth. In addition, a PhD-level licensed clinical psychologist who is a member of the Motivational Interviewing Network of Trainers (MINT), will provide initial and ongoing training to the coaches. CONNECT coaches will spend one day per week in their assigned high schools. Each semester, the CONNECT coaches will meet individually with all students in the study cohort for approximately 10 to 15 minutes in a private school office or via Zoom. For students habitually absent from school, coaches will schedule sessions via electronic communications (e.g., Zoom, texts, calls, private messages via encrypted social media such as Whatsapp), and conduct face-to-face meetings in private community settings such as Cherokee Nation clinics.

During the CONNECT session, coaches will conduct screening, assess risk, and initiate MI. MI will be used with low-risk students to affirm the student's decision to avoid drug use and develop personal goals to remain drug-free. For students assessed at moderate risk, MI will be conducted to enhance motivation to avoid riskier situations with access to drugs, and decrease drug use. For high-risk students, coaches will facilitate connection to substance use and mental health treatment facilities, and link students and their guardians to relevant social service resources. The full complement of Cherokee Nation health services are available to any AI youth. Non-Indian youth will be linked with other community services. Additionally, coaches will have a follow-up appointment within one month to monitor each moderate- and high-risk student, adjust goals, normalize setbacks, explore ambivalence about changing relevant behaviors, and provide ongoing support.

CONNECT coaches will implement skill training, Youth Mental Health First Aid (<https://www.mentalhealthfirstaid.org/about/>), for teachers, other school staff, parents and community members to expand school and community natural helpers and build a network of trusted support for youth. Youth Mental Health First Aid develops skills to identify youth with mental health and substance use concerns, and how to communicate and intervene to provide support.

Communities Mobilizing for Change and Action (CMCA). Ten part-time local community organizers will be hired, one in each intervention community, to focus on reducing the supply of drugs to youth. Other key goals of CMCA are to empower citizens to make change in their communities, enhance social connections, and support drug-free norms. CMCA organizers will be supervised, guided, and supported by team members with expertise in community organizing and opioid and other drug prevention and harm reduction. Community organizers will attend a series of project trainings, including ongoing skill-based training. Following initial training and baseline data collection, each organizer will initiate the CMCA organizing six-stage process in their community. The six-stage process includes (1) assessment of community conditions, norms, and practices; (2) building a citizen-led Action Team; (3) expanding the

base, which involves understanding the power structure, finding additional passionate advocates, strategic thinking and planning, constituency building, and building a power base for taking action; (4) developing an action plan; (5) implementing the action plan; and (6) assessing initial results, celebrating accomplishments and refining planned next steps for maintaining effort and institutionalizing changes. Potential actions will focus on reducing easy access of alcohol and other drugs to youth and may include educational and advocacy campaigns, drug take-back initiatives, strategies to reduce social sources, and collaborations with law enforcement and other community institutions to prevent and reduce easy access of drugs to youth. The organizing approach is about empowering citizens, including parents, to influence relevant institutional leaders to take actions for structural and sustainable change. Strategic planning meetings with project leadership and organizers will occur multiple times a year and incorporate additional training for the community organizers.

Media. Media campaigns will support the CONNECT and CMCA interventions and will include: (1) earned media (aka “media advocacy” or generated news coverage); (2) strategically designed, timed, and placed paid media; and (3) social media venues such as Facebook, Twitter, Instagram and lesser known locally used platforms. Media campaigns will be designed for different segments of the community, including family and other social networks important to youth.

Primary and secondary outcomes

Data collection. Variables of interest will be measured with a self-report survey of the cohort of youth ages 15 to 17 at baseline and followed over three years through their transition out of high school (ages 18 to 20). The first survey will be conducted prior to intervention initiation during the fall of the cohort’s 10th grade. Six follow-up surveys will occur, one every six months, beginning in the spring of their 10th grade; follow-ups begin immediately following intervention initiation, and end six months following high school graduation. Youth surveys will be administered via a secure web-based survey using project tablets or personal devices. Location of the self-report survey administration will include home, school, or other private location. Survey data collection will be incentivized and vary by location.

Outcome measures. The survey includes common measures developed in collaboration with the HEAL Prevention Cooperative, ten research projects and a coordinating center funded by NIDA, and were heavily drawn from the PhenX Toolkit substance use patterns – adolescent module, measured with standard items from the Monitoring the Future (MTF) study [32]. Primary outcomes are past 30 days of alcohol, marijuana, and prescription opioid misuse (“without a doctor’s prescription or differently than how a doctor or medical provider told you to use it”). Secondary outcomes of key mediators (i.e., mechanisms) include perceived availability of drugs, social support, social normative beliefs, normative estimates, and self-efficacy. In addition to key outcomes, we will include measures of substance use related problems (i.e., missed responsibilities, social problems), comorbidities (i.e., depression, anxiety, pain), and possible intervention effect moderators (e.g., age, gender, race/ethnicity, Native American tribal identity, measures of economic and food security).

Fidelity assessments

Field staff will use laptop computers loaded with research-team-designed management information systems that facilitate their work as well as provide ongoing measures of implementation and progress. Forms include easy-to-use drop-down menus that provide response options for each domain to minimize time burdens associated with completing paperwork and to improve overall efficiency. CONNECT coaches will complete interaction forms following each one-on-one encounter. Coaches will document risk level, behavioral goals, dates of follow-up appointments, and referrals made, if applicable. To assess MI skill among the coaches, during training sessions, coaches will complete mock CONNECT sessions with an actor who portrays a typical student. As in our previous trial, to measure fidelity, mock encounters will be video recorded, coded, and rated using the Motivational Interviewing Treatment Integrity Coding System [33]. We will survey high school teachers to assess confidence, skills, and practices of strategies covered in the Youth Mental Health First Aid training. CMCA organizers will document details of all community contacts, action team members, meetings, actions/events, and proximal organizing outcomes achieved. Data will be uploaded each week and reviewed by the project team and used in strategic planning meetings with leadership and field staff. Finally, we will survey the citizen Action Team members to assess changes in social capital. Additionally, we will assess other unrelated prevention activities as documented by a key school representative on an annual survey.

Cost assessments

In collaboration with the HEAL Prevention Cooperative (HPC) and coordinating center, we will document costs and collaborate on cost-effectiveness analysis. The cost instrument developed with the HPC economic workgroup will be used to capture activity-based costing. Implementation costs will be captured prospectively by including measures of resource use into intervention process evaluation forms. We will collect data on several measures, including: (1) minimum staff to implement the project; (2) local needs (e.g., office space, telephone, local travel); (3) training and technical assistance; and (4) opportunity and marginal costs (e.g. support from volunteers).

Measures

Measures evaluate community and school context, implementation outcomes, and youth outcomes including hypothesized mediators and moderators. Table 2 displays all study measures, and Supplementary File 1 provides additional detail for the youth outcomes measures.

Table 2
Study measures by construct.

Construct	Measure	Type	Informant	Timing
Context				
School	School size, race/ethnic composition, etc	Record	Record	Year 1
Community	Library, churches, city government, police, etc	Record	Record	Year 1
Implementation				
Connect implementation	Session attended, risk level, behavioral goals, use of MI	Session form	Connect coach	Year 2–4
Connect MI fidelity	Motivational Interviewing Treatment Integrity Coding System	Videotaped coding of Connect coach MI skills	Observer	Year 2–4
Teacher adoption of practices	Confidence, skills, and practices	Survey	Teachers	Year 2–4
CMCA implementation	Contacts, action team members, meetings, actions/events, and outcomes achieved	Access database forms	CMCA organizers	Year 2–4
CMCA implementation	Participation, social capital	Survey	Action Team members	Year 2–4
Other prevention activities	Curriculum, screenings, parent education, community prevention, media, etc	Survey	School representative	Year 2–4
Youth Measures				
Demographics	Age, gender, race/ethnicity, tribal citizenship, tribal identity, free/reduced price lunch	Survey	Youth	Year 2–5
Mediators	Social support, perceived availability of drugs, social normative beliefs, self-efficacy, normative estimates	Survey	Youth	Year 2–5
Other	Depression, anxiety, pain, future aspirations	Survey	Youth	Year 2–5
Primary outcomes	Past 30 day use of alcohol, marijuana, prescription opioid misuse	Survey	Youth	Year 2–5

Data analytic plan

This trial consists of “doubly repeated” measures—repeated measures nested within each student, plus students are nested within schools. To account for both the clustering effect of students nested within schools and repeated measures nested within student, intervention effects on secondary and drug use outcomes will be estimated with generalized linear mixed models specifying a random intercept for each school and allowing within student residuals to be correlated over time. To estimate change in secondary (e.g., perceived drug availability, norms, social support) and primary (e.g., past month number of days of opioid use without a prescription, marijuana use) outcomes due to the intervention, we will begin by analyzing models of the following form: $g(y) = \beta_0 + \beta_1 \text{TimeL} + \beta_2 \text{IntG} + \beta_3 \text{TimeL} * \text{IntG}$ where $g()$ represents the appropriate link function for outcome y , TimeL is a linear variable representing the survey wave, and IntG is an indicator for the intervention group. The parameter of primary interest is β_3 , the difference in slope between the intervention and control group. The link function $g()$ will be chosen to properly model the distribution for each outcome. If it is found that a linear slope does not fit the shape of the intervention curve well, we will fit models of the following form: $g(y) = \beta_0 + \beta_{1-5} \text{TimeFE} + \beta_6 \text{IntG} + \beta_{7-11} \text{TimeFE} * \text{IntG}$. This model is similar to the previous model except the linear variable for time has been replaced with a series of fixed effects (TimeFE) to allow for a non-linear pattern of change over time. For this model, the parameters β_{7-11} must be tested jointly using a likelihood ratio test comparing the proposed model and a model where β_{7-11} are fixed to 0. Attrition will be accounted for in all analyses by full information maximum likelihood [34].

Power

The proposed analytic approach is well-powered to achieve primary study aims. We estimated the statistical power to detect a change in the trajectory over time between intervention and control conditions using PROC GLMPower in SAS v9.4. To account for clustering within school and autocorrelation within student, we estimate power for a multivariate model equivalent to our planned “doubly repeated” mixed effects models previously described. Final multivariate correlation matrices are calculated by taking the Kronecker product of a compound symmetric matrix for students nested within schools ($\text{ICC} = 0.01$ to 0.05) and a LEAR matrix for survey waves nested within student ($\rho = 0.3$, $\delta = 0.2$). The specified LEAR structure allows within student autocorrelation to decay more slowly than the AR(1) structure, which is appropriate for adolescent substance use behaviors [35]. To be conservative in our power estimates we treat time as a fixed effect in all power calculations. Should we determine that linear time trends provide an appropriate fit, power will exceed what is reported below. All power estimates assume a type-1 error rate of 0.05 and 20 balanced schools. While we expect low attrition rates due to planned follow-up procedures, we conservatively assume a 20% attrition rate by specifying the within school sample size as 46 (an average of 57 10th graders per school times 0.8). Our primary and secondary outcomes are continuous scales or count data. We approximate power for both by treating all outcomes as Gaussian. Assuming a linear intervention effect through post-high school follow-up, we are

powered at the 0.8 level to detect a standardized mean difference of 0.32 at an ICC of 0.01 and 0.47 at an ICC of 0.05 at the end of follow-up.

Monitoring

The Principal Investigator will be responsible for monitoring the safety and efficacy of this trial, executing the Data and Safety Monitoring (DSM) plan, and complying with the reporting requirements to the funding agency and Cherokee Nation IRB. The annual DSM report will include the participants' sociodemographic characteristics, expected versus actual recruitment rates, any regulatory issues that occurred during the past year, summary of adverse events and serious adverse events, and any actions or changes with respect to the protocol. Reporting guidelines will be followed for any unanticipated adverse events and serious adverse events. The investigators have developed a detailed plan for protection of data, mandatory reporting, and addressing a distressed participant that will be applied during the study. The Cherokee Nation IRB will review and approve all products for dissemination, including presentations and publications.

Discussion

Innovation

The innovation of the trial is summarized with three core ideas: combination, integration, and partnership. We combine effective strategies from different levels of influence in socio-ecological models (individual, school, family, community). We combine our longstanding experience and success with adolescent drug prevention with a renewed focus on the developmentally critical (especially for opioid misuse) transition from adolescence to adulthood—from high school to post-secondary education, training, and employment opportunities and into independent adult roles in the community, tribe and society. We integrate two well-designed, tested and effective interventions—CMCA and CONNECT—which to date have been treated as independent interventions (and both found to be effective), into a single mutually-reinforcing intervention supported with strategic media. The intervention is theoretically informed, drawing from an integration of diverse theories from psychological, social-psychological, sociological, social work, public policy, and political science fields. This enhances likelihood of: improving individuals' resistance to drug misuse; altering the functioning of social groups; changing structures, procedures and processes of local institutions; and strengthening community connectedness and anti-drug-misuse norms. Importantly, we administer and oversee implementation of the intervention through Cherokee Nation Behavioral Health, enhancing uptake of the intervention to other sites after the research trial, and substantially improving long-term sustainability. Finally, the proposed trial is innovative because of the depth of partnership. The Cherokee Nation reservation, unlike other reservations, includes citizens of other AI tribes as well as a substantial White population. The intervention will be universally implemented to all, and the project creates the necessary structures and processes to help serve the needs of all (e.g., referrals for special services or treatment). The community environments are complex, with overlapping jurisdictions and responsibilities of the Cherokee Nation with municipalities, counties, school districts,

policing agencies, and health systems. The Cherokee Nation has longstanding patterns of partnership across these elements that will be further enhanced during implementation of the trial.

Limitations

The current study only recruits schools within or near the boundaries of the Cherokee Nation in northeastern Oklahoma, and therefore the generalizability may be limited to rural communities in or near American Indian reservations. The outcome evaluation is limited to one cohort of youth who will be exposed to the school and community interventions, therefore the outcomes will not capture potential effects of the community intervention on other youth. The delayed-intervention control group will likely be implementing other prevention activities, which we will measure with an annual survey. Therefore the effects of the intervention are in comparison to prevention as usual.

Conclusion And Impact

In summary, the proposed trial is significant because it: (1) focuses on primary prevention—reducing initiation and early use—rather than secondary prevention to reduce harm among users, (2) focuses on at-risk rural and AI populations, (3) is conducted in close collaboration with the Cherokee Nation (the largest tribe), (4) enhances previously tested and effective CMCA and CONNECT interventions specifically for opioid misuse and other drug prevention, and (4) evaluates effects and mechanisms of the enhanced intervention using a rigorous randomized cluster trial with well-established measurement and implementation processes.

Trial Status

ClinicalTrials.gov Identifier: NCT04839978. First posted and registered April 9, 2021, last update posted May 6, 2021. Recruitment will begin September 2021 and end August 2024.
<https://clinicaltrials.gov/ct2/show/NCT04839978>

Declarations

Ethics approval and consent to participate

This project was approved by the Cherokee Nation Institutional Review Board (IRB).

Consent for publication

The Cherokee Nation IRB reviewed and approved this manuscript for publication. A model consent form is available on request.

Availability of data and materials

Please contact the lead author for more information. The researchers at Emory University, in partnership with Cherokee Nation Behavioral Health, agree to securely collect, and store project data, and further agree to share the study data, provided all data requests are reviewed and approved by the Cherokee Nation IRB. It is the responsibility of any external party requesting access to project data to request in writing to the project PI the specific data requested, and to apply to the Cherokee Nation IRB for such access according to procedures promulgated by the Cherokee Nation. Further, any such access is conditional on meeting all requirements specified by the Cherokee Nation IRB.

Trial results will be disseminated through scientific publications, professional conferences, written reports, in-person and Zoom meetings, and other to community partners and study participants. Cherokee Nation IRB reviews and approves all dissemination products.

Competing interests

All authors declare that they have no competing interests.

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Authors' contributions

KAK, TKK, JRS, MDL, HLFC, and ACW developed the overarching scientific aims and design of the project. KAK, TKK, JRS, MDL, BJL, CMB, ALW, HLFC, and ACW participated in the development and operationalization of the study methods and worked with KAK to obtain institutional review board approval. KAK, TKK, JRS, and BJL are supporting study recruitment. TKK, BJL, CMB, ALW are supporting data collection. KAK, JRS, BJL, KA, ANL, CMB, DWP, LJM, HLFC, and ACW developed study implementation strategies. All authors contributed to the development, drafting, or review of the manuscript. All authors approved the final manuscript.

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References

1. Case A, Deaton A. Mortality and morbidity in the 21st century. *Brookings Pap Econ Act*. 2017: Johns Hopkins University Press; 2017. pp. 397–476.
2. Committee on Rising Midlife Mortality Rates and Socioeconomic Disparities, Committee on National Statistics, Committee on Population, Division of Behavioral and Social Sciences and Education. National Academies of Sciences, Engineering, and Medicine. High and Rising Mortality Rates Among Working-Age Adults. Harris KM, Majmundar M, Becker T, editors. Washington (DC): National Academies Press (US); 2021.
3. Venner KL, Donovan DM, Campbell ANC, Wendt DC, Rieckmann T, Radin SM, et al. Future directions for medication assisted treatment for opioid use disorder with American Indian/Alaska Natives. *Addict Behav*. 2018;86:111–7.
4. Komro KA. Preventing Risk for “Deaths of Despair” Among American Indian Youths: Unanswered Questions for Future Research. *Am. J. Public Health*. 2018. p. 973–4.
5. Chiappini S, Guirguis A, John A, Corkery JM, Schifano F. COVID-19: The Hidden Impact on Mental Health and Drug Addiction. *Front Psychiatry*. 2020;11:767.
6. Zaami S, Marinelli E, Varì MR. New Trends of Substance Abuse During COVID-19 Pandemic: An International Perspective. *Front Psychiatry*. 2020;11:700.
7. Volkow ND. Collision of the COVID-19 and Addiction Epidemics. *Ann Intern Med*. 2020;173:61–2.
8. Products - vital. statistics rapid release - provisional drug overdose data [Internet]. 2021 [cited 2021 May 5]. Available from: <https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm>.
9. Czeisler M, Lane RI, Petrosky E, Wiley JF, Christensen A, Njai R, et al. Mental Health, Substance Use, and Suicidal Ideation During the COVID-19 Pandemic - United States, June 24–30, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:1049–57.
10. Horigian VE, Schmidt RD, Feaster DJ. Loneliness, Mental Health, and Substance Use among US Young Adults during COVID-19 [Internet]. *Journal of Psychoactive Drugs*. 2021. p. 1–9. Available from: <http://dx.doi.org/10.1080/02791072.2020.1836435>.
11. Volkow ND, Han B, Einstein EB, Compton WM. Prevalence of Substance Use Disorders by Time Since First Substance Use Among Young People in the US. *JAMA Pediatr* [Internet]. 2021; Available from: <http://dx.doi.org/10.1001/jamapediatrics.2020.6981>.
12. Wall M, Cheslack-Postava K, Hu M-C, Feng T, Griesler P, Kandel DB. Nonmedical prescription opioids and pathways of drug involvement in the US: Generational differences. *Drug Alcohol Depend*. 2018;182:103–11.

13. McCabe SE, Veliz PT, Boyd CJ, Schepis TS, McCabe VV, Schulenberg JE. A prospective study of nonmedical use of prescription opioids during adolescence and subsequent substance use disorder symptoms in early midlife. *Drug Alcohol Depend.* 2019;194:377–85.
14. Kingery KL. County Health Rankings & Roadmaps. 13: University Library System, University of Pittsburgh; 2018. pp. 259–63.
15. Scholl L, Seth P, Kariisa M, Wilson N, Baldwin G, Drug and Opioid-Involved Overdose Deaths – United States, 2013–2017 [Internet]. *MMWR. Morbidity and Mortality Weekly Report.* 2018. Available from: <http://dx.doi.org/10.15585/mmwr.mm675152e1>.
16. Health services [Internet]. [cited 2021 Apr 13]. Available from: <https://health.cherokee.org>.
17. Health Services [Internet]. [cited 2021 Apr 13]. Available from: <https://health.cherokee.org/services-and-programs/behavioral-health>.
18. Komro KA, Livingston MD, Wagenaar AC, Kominsky TK, Pettigrew DW, Garrett BA, et al. Multilevel Prevention Trial of Alcohol Use Among American Indian and White High School Students in the Cherokee Nation. *Am J Public Health.* 2017;107:453–9.
19. Livingston MD, Komro KA, Wagenaar AC, Kominsky TK, Pettigrew DW, Garrett BA. Effects of Alcohol Interventions on Other Drug Use in the Cherokee Nation. *Am J Public Health.* 2018;108:259–61.
20. Oesterle S, Kuklinski MR, Hawkins JD, Skinner ML, Guttmanova K, Rhew IC. Long-Term Effects of the Communities That Care Trial on Substance Use, Antisocial Behavior, and Violence Through Age 21 Years. *Am J Public Health.* 2018;108:659–65.
21. Spoth R, Redmond C, Shin C, Greenberg MT, Feinberg ME, Trudeau L. PROSPER delivery of universal preventive interventions with young adolescents: long-term effects on emerging adult substance misuse and associated risk behaviors. *Psychol Med.* 2017;47:2246–59.
22. Havens JR, Young AM, Havens CE. Nonmedical prescription drug use in a nationally representative sample of adolescents: evidence of greater use among rural adolescents. *Arch Pediatr Adolesc Med.* 2011;165:250–5.
23. Fraser M, Plescia M. The Opioid Epidemic’s Prevention Problem. *Am J Public Health.* 2019;109:215–7.
24. Moulton LH. Covariate-based constrained randomization of group-randomized trials. *Clin Trials.* 2004;1:297–305.
25. Carter BR, Hood K. Balance algorithm for cluster randomized trials. *BMC Med Res Methodol.* 2008;8:65.
26. Li F, Lokhnygina Y, Murray DM, Heagerty PJ, DeLong ER. An evaluation of constrained randomization for the design and analysis of group-randomized trials. *Stat Med.* 2016;35:1565–79.
27. National Center for Education Statistics. National Center for Education Statistics Data Explorer [Internet]. 2020 [cited 2021 Mar 18]. Available from: <https://nces.ed.gov/>.
28. Oklahoma State Department of Education. Oklahoma School Report Cards [Internet]. Oklahoma Schools. 2020 [cited 2021 Mar 18]. Available from: <https://oklaschools.com/>.

29. OK State Department of Education. Annual Incident and Suspension Reports [Internet]. OK State Department of Education Public Records. 2020 [cited 2021 Mar 18]. Available from: <https://sde.ok.gov/documents/2016-11-10/annual-incident-report>.
30. Oklahoma Medical Marijuana Agency. OK Medical Marijuana Dispensary List [Internet]. OMMA. [cited 2021 Mar 18]. Available from: https://oklahoma.gov/content/dam/ok/en/omma/docs/business-lists/omma_dispensaries_list.pdf.
31. Oklahoma Board of Behavioral Health Licensure. OK State Board of Behavioral Health- LPC License Search [Internet]. State Board of Behavioral Health. 2021 [cited 2021 Mar 18]. Available from: <https://obbhl.us.thentiacloud.net/webs/obbhl/register/#>.
32. Welcome to the MTF website [Internet]. [cited 2021 Apr 13]. Available from: <http://www.monitoringthefuture.org>.
33. Miller WR, Moyers TB, Arciniega L, Ernst D, Forcehimes A. Training, supervision and quality monitoring of the COMBINE Study behavioral interventions. J Stud Alcohol Suppl. 2005;188–95; discussion 168–9.
34. Allison PD. Statistical Horizons. Handling missing data by maximum likelihood [Internet]. [cited 2021 Apr 26]. Available from: <https://statisticalhorizons.com/wp-content/uploads/MissingDataByML.pdf>.
35. Simpson SL, Edwards LJ, Muller KE, Sen PK, Styner MA. A linear exponent AR(1) family of correlation structures. Stat Med. 2010;29:1825–38.

Figures

Figure 1

Study Design

Figure 2

Community and school selection, recruitment, allocation, and participant enrollment.

Supplementary Files

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