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Publication Date

2021-09-01

DOI

10.1016/j.cct.2021.106523

Peer reviewed

HHS Public Access

Author manuscript

Contemp Clin Trials. Author manuscript; available in PMC 2022 September 01.

Published in final edited form as:

Contemp Clin Trials. 2021 September ; 108: 106523. doi:10.1016/j.cct.2021.106523.

Optimizing Scalable, Technology-Supported Behavioral Interventions to Prevent Opioid Misuse Among Adolescents and Young Adults in the Emergency Department: A Randomized Controlled Trial Protocol

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Conflict of Interests:
The authors do not have any personal financial interests related to the subject matters discussed in this manuscript.
Dr. Glantz's role on this study is through his involvement as a Science Officer on UG3/UH3 DA050173. He had no involvement in the other cited grants.

NCT Registration: NCT04550715

Trial Registration: ClinicalTrials.gov #00177625. University of Michigan HUM00177625

Declaration of interests
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abstract

Preventing opioid misuse and opioid use disorder is critical among at-risk adolescents and young adults (AYAs). An Emergency Department (ED) visit provides an opportunity for delivering interventions during a rapidly changing opioid landscape. This paper describes pilot data and the protocol for a 2 x 2 factorial randomized controlled trial testing efficacy of early interventions to reduce escalation of opioid (prescription or illicit) misuse among at-risk AYAs. Interventions are delivered using technology by health coaches. AYAs ages 16-30 in the ED screening positive for prescription opioid use (+≥1 risk factor) or opioid misuse will be stratified by risk severity, sex, and age group. Participants will be randomly assigned to a condition at intake, either a live video health coach-delivered single session or a control condition of an enhanced usual care (EUC) community resource brochure. They are also randomly assigned to one of two post-intake conditions: health coach-delivered portal-like messaging via web portal over 30 days or EUC delivered at 30 days post-intake. Thus, the trial has four groups: health coach-delivered session+portal, health coach-delivered session+EUC, EUC +portal, and EUC+EUC. Outcomes will be measured at 3-, 6-, and 12-months. The primary outcome is opioid misuse based on a modified Alcohol Smoking and Substance Involvement Screening Test. Secondary outcomes include other opioid outcomes (e.g., days of opioid misuse, overdose risk behaviors), other substance misuse and consequences, and impaired driving. This study is innovative by testing the efficacy of feasible and scalable technology-enabled interventions to reduce and prevent opioid misuse and opioid use disorder.

Keywords

prevention; opioids; adolescents; emerging adults; intervention

1.0 INTRODUCTION

Preventing and reducing risky opioid misuse among older adolescents and young adults (AYAs; hereafter ages 16-30) is critical given that peak misuse rates and associated

morbidity and mortality (e.g., overdose; opioid use disorder[1–3]) coincide with this developmental period. Nationally, past-year *prescription opioid use* ranges from 19.7% for ages 16-17 to 28.2% for ages 26-29, whereas past-year *opioid misuse* ranges from 3.4% to 5.8%, for these age groups respectively.[4] Nearly one in three adolescents who report prescription opioid misuse by age 18 transition to heroin use in young adulthood.[5] AYAs who misuse opioids are at increased risk for adverse health outcomes[6] such as fatal/non-fatal injury, overdose, and opioid use disorder, warranting approaches designed to mitigate these consequences.

U.S. emergency departments (EDs) have over 130 million visits annually[7] and the ED is a key location to bridge the divide to increase access to services and connection to the larger health system among at-risk AYAs who often are not continually connected to healthcare providers.[8] Despite the current US opioid crisis, early interventions for AYAs focused on preventing opioid misuse/opioid use disorder are generally lacking in healthcare settings and research has called for more robust strategies, including those that use health coaching, focused on opioids.[9] Although ED-based brief motivational interventions delivered by counselors of varying training backgrounds reduce other substance use/consequences among AYAs[10–18], their impact when tailored for AYA opioid misuse remains to be seen, lending to the focus of this trial.

Our emphasis on tailored motivational interventions is underscored by prior work finding primary efficacy of a single-session brief motivational intervention in reducing opioid misuse and overdose risk behaviors in adult ED patients.[19] We also demonstrated the secondary efficacy of ED and primary care-based brief interventions on reducing AYAs' prescription drug misuse (primarily opioids[20–22]). We blended and packaged the content from these promising interventions as an initial intervention strategy in this trial. Our delivery approach for this early intervention is designed to increase the likelihood of implementation in busy medical settings, by using remote health coaches (e.g., in a telemedicine call center), allowing for real-time personalization and maximizing shelf-life to adapt to this rapidly changing crisis, with limited impact on ED staff.

Due to the short-term and modest effects of the prior interventions mentioned above, we are also testing a strategy wherein health coaches are providing MI-based interventions for 30 days post-ED visit using a chat-based web portal. This portal mirrors the messaging style, and increasingly the function, of health systems' patient portals, which promotes future implementation and scalability. Indeed, our prior work demonstrated the potential of this approach by delivering motivational interviewing-based (MI)[23] content in a portal-like platform to enhance motivation to seek mental health services for suicide prevention[24] and others have used a portal to deliver alcohol-related feedback.[25]

After evaluating feasibility and acceptability (section 2.1.1) of our ED-initiated interventions among AYAs screening positive for recent *prescription opioid use* with at least one risk factor or prescription or illicit *opioid misuse* we initiated a 2 x 2 factorial randomized controlled trial (RCT). The primary aim of the RCT is to evaluate the efficacy of 1) an intake condition of a remote health coach-delivered single session brief motivational intervention vs. a control condition of an enhanced usual care (EUC) community resource brochure; and,

2) post-intake health coach-delivered portal-like messaging via a web portal over 30 days or EUC delivered at 30 days post-intake. Testing the relative efficacy of the health coach session, health coach session combined with the portal, or the portal intervention alone has high potential for public health impact by identifying the most effective combination of strategies to reduce primary outcomes of opioid misuse severity. We will also examine intervention efficacy on other opioid outcomes (e.g., days of opioid misuse, overdose risk behaviors), other substance misuse and consequences, and impaired driving. Further, we will also measure intervention costs and identify moderators/mediators of efficacy. In this paper, we describe the RCT protocol with a focus on evaluation of primary and secondary outcomes.

2.0 METHODS

2.1 Design Overview.

We are testing the efficacy of behavioral interventions as secondary prevention for opioid misuse and opioid use disorder among AYAs in a 2 x 2 factorial RCT design with two intake and two post-intake conditions. Conditions delivered at intake are: 1) a single video-delivered health coach session, and 2) an EUC control condition of a community resource brochure. Post-intake conditions are: 1) portal messaging that lasts for 30 days, or 2) EUC control brochure delivered at 30 days. This combination effectively results in 4 groups as shown in Figure 1 (see Figure 2 for additional details). The health coach session occurs during intake and the portal begins at intake (after delivery of first-stage condition) and occurs over the following 30 days. Depending on randomization, the EUC resource brochure is either delivered at intake or 30 days later (or both). EUC essentially functions as a control condition, with the provision of minimal resources that exceed the current standard of care in the ED pertaining to opioid screening and prevention as done in a number of prior ED-based studies.[22,26–28]. In total, we seek to enroll 1170 ED patients ages 16 to 30 (Figure 1). Recruitment occurs either in-person or remotely, a secondary recruitment approach that was added because of restrictions on in-person research activities during the COVID-19 pandemic. All procedures are IRB approved.

2.1.1 Intervention Piloting—As part of our funding mechanism and with IRB approval, we piloted the interventions and EUC described in detail below (section 2.5) in the Spring of 2020, with N = 40 AYAs enrolled with informed consent/assent (parental consent) and the same trial eligibility criteria described below. Each participant received the EUC at enrollment, the health coach session, 30 days of portal messaging, and a 1-month follow-up invitation e-mail (including a webpage link to EUC resources). After enrolling the first 10 participants using ED-based recruitment methods, we paused recruitment to refine interventions based on participants' feedback. During this pause, in-person recruitment efforts were suspended due to the COVID-19 pandemic, and the remaining 30 participants were recruited remotely after their ED visit and all interventions were delivered remotely in private from staff homes to participants' homes.

Among the participants who participated in pilot testing the health coach session, 38 provided acceptability ratings. Their intervention satisfaction was $M = 9.3$ ($SD = 1.3$)

on a 10-point scale with 10 being the highest possible rating. Similarly, on a 10-point scale, ratings for recommending the intervention were $M = 9.0$ ($SD = 1.9$). Fidelity coding of selected sessions was based on the Motivational Interviewing Treatment Integrity Code[33] with fidelity exceeding "fair" thresholds, and nearly all markers exceeding "good" thresholds. These included the following means: $M = 4.3$ relational scale, $M = 3.9$ technical score, $M = 71.5\%$ complex reflections, and $M = 1.7{:}1$ reflection/question ratio.

Next with regard to the portal, among our first 10 participants, portal engagement was lower than expected ($M = 3.3$ [SD = 2.8] replies from participants) with only 60% replying at all. Thus, we used participant feedback to make several functional and design changes prior to recruiting the next 30 participants. These changes included adding a "remember me" function to avoid needing to remember a password, updating the look and feel of the portal, adding use of an emoji avatar chosen by participants, branded token items valuing ~$1 mailed weekly (e.g., stress balls, etc.). We also evaluated use of an incentive structure for portal messaging with the final 30 participants. Thus, we enrolled 10 participants each into cohorts: a) no incentive for message replies, b) $1 incentive for each reply with ability to earn up to $20, and c) $5 incentive for each reply with ability to earn up to $20. Engagement, as measured by number of replies from participants, was higher in these latter cohorts. The no incentive cohort had a $M = 11.8$ ($SD = 7.6$) messages received with 100% replying, the $1 incentive group had $M = 10.0$ ($SD = 6.9$) messages received with 80% replying, and the $5 incentive group had $M = 15.6$ ($SD = 9.9$) messages received with 100% replying. Given that functional and design changes in the portal appeared to result in increased engagement without the use of additional incentives, we elected to not incentivize participation in the planned RCT, especially since there would be additional challenges associated with later implementation of incentives within healthcare systems.

Finally, among 37 pilot participants who provided feedback ratings for the portal, ratings of satisfaction were $M = 8.5$ ($SD = 1.7$) and recommendation were $M = 8.9$ ($SD = 1.6$), on a 10-point scale with 10 being the highest rating. Modified MITI fidelity coding for complex reflections and reflection-to-question ratio exceeded benchmarks such that were on average 59.5% complex reflections and the average reflection-to-question ratio was 2.9:1.

Overall, the feasibility of our pilot testing supported the inclusion of the intervention conditions in the planned RCT. The acceptability data provided by participants at follow-up was promising, particularly given refinements to the portal condition, and staff demonstrated acceptable fidelity to the intervention model.

2.2 RCT study setting

Participants are recruited from the Michigan Medicine pediatric (ages 20 years and under) and adult EDs (ages 21 years and greater) in Ann Arbor, Michigan. Combined, these EDs have about 100,000 visits per year and are located in adjacent, but separate hospitals and maintain independently functioning systems of triage, medical staffing, and physical space allocation. Recruiting from both EDs enhances generalizability to pediatric and adult ED settings. Historically, the average ED length of stay as been 3-4 hours which facilitates completion of in-person research protocols during the visit, although the COVID-19 pandemic has altered ED patient flow. Currently, there are no opioid-focused prevention

programs in the study setting and opioid-related clinical care focuses primarily on treatment referrals and prescription monitoring.

2.3 RCT exclusions and eligibility

We attempt to recruit English-speaking patients ages 16-30 presenting to the ED for any reason (except as noted below) in-person or remotely (e.g., email, call, text, letter obtained from the electronic health record [EHR]) to complete an eligibility screening. Staff approach participants in the ED, and remote recruitment is used when staff are unable to recruit in the ED (e.g., during COVID-related shutdowns) or to supplement in-person recruitment because of physical distancing limitations on approaching patients with suspected COVID and the number of staff who can be present at any one time due to COVID-related restrictions. When approaching potential participants, they must be medically and cognitively able (e.g., conscious, not intubated) to provide consent/assent; thus patients presenting with acute substance intoxication are excluded until able to consent. Individuals presenting to the ED with a chief complaint of acute sexual assault or acute suicidality will be excluded from screening. Those presenting with a current cancer diagnosis or currently receiving cancer treatment (which would require unique intervention content pertaining to opioids and pain management) and pregnant women will also be excluded (based on chief complaint and/or screening survey). AYAs who participated in our pilot study described below or who may be taking part in other current behavioral intervention trials at this study site are also excluded (currently there are no ongoing trials).

Screened participants are eligible for the trial based on past 12-month prescription opioid use plus at least 1 other risk factor (defined as recent misuse of cannabis or illicit drugs, other prescription drug misuse, binge drinking, depression or suicidality), or 12-month opioid misuse (prescription or illicit [e.g., heroin, fentanyl]) as described in the measures below (section 2.7.1). Screened individuals reporting injecting drugs or screening as high risk for current opioid use disorder based on a NIDA-Modified ASSIST V2[29–32] score of 27+ are excluded due to the study focus on prevention of development of opioid use disorder. These individuals are instead referred for treatment; staff direct them to options listed in study resource brochure if recruited remotely and if in recruited in-person staff offer referral to ED social worker.

2.4 Procedures for enrollment, consent, randomization, and assessments

All procedures herein have been piloted in the study setting and among AYAs, including consenting and enrolling minors. Research assistants identify patients ages 16-30 via the electronic health record (EHR) and tracking system, with a waiver of HIPAA authorization. Patients who meet screening exclusion criteria are not approached. Staff approach screening eligible patients based on triage time/status (i.e., for in-person recruitment) or discharge date/time (i.e., for remote recruitment) using a standard script. Two-stage consent for ages 18+ and parental consent/child assent (ages 16-17) rare obtained for screening and, subsequently, the RCT. Staff review limits to confidentiality (e.g., acute suicidality risk) and study procedures during consenting/assenting. Specifically, parents are consented concurrently for screen and baseline (i.e., explaining and obtaining permission for procedures in the event their child is eligible for the RCT). Subsequently, youth assent

is obtained for screen and baseline. Study data is not shared with parents or guardians and confidentiality would only be broken in the case of acute risk, such as acute suicidality, homicidality, or child abuse, to preserve adolescents' or others' safety.

For in-person recruitment, research staff approach ED patients ages 16-30 (and parents, when needed) for consent/assent to self-administer a brief web-based screening survey on iPads. Surveys are paused during medical procedures and consultations such as x-rays, assessments, and blood draws. For remote recruitment, research assistants contact (e.g., email, call, text, letter) ED patients ages 16-30 after discharge for consent/assent to complete the screening survey on their personal device or by phone. Participants screened in person receive a gift valuing $1.00 (e.g., earbuds, lotion, etc.) for survey completion.

AYAs meeting eligibility criteria above are invited to participate in the RCT. After consenting/assenting, RCT participants complete a baseline survey (either in-person in the ED or remotely) and are randomized to conditions. Randomization is stratified by sex, age (16-25; 26-30), and opioid risk severity (based on highest heroin/prescription opioid ASSIST score): none (0) or higher (total = 1-26; 27+ excluded, as described above) and occurs in blocks of 8 within strata to equalize over time. Randomization is computer-generated in Qualtrics and is not be known by recruitment staff until after completion of the baseline survey when staff run the randomization program to reveal condition. Staff then orient participants to their assigned condition. Because this is a behavioral intervention where participants are receiving counseling interventions, participants and coaches are not blind to their condition.

Participants then receive their assigned intake condition at intake (health coach session or EUC) and are then oriented to their post-intake condition (Portal or EUC). If needed, those unable to complete all intake activities in the ED may complete them in person, by telephone, or video call; these activities are scheduled prior to leaving the ED. Participants who join the study remotely, or who do not complete enrollment during the ED visit, may have up to 30 days to complete intake activities. Enrolled participants receive a token gift (i.e., carabiner with study name) in-person or by mail. Participants are asked to complete follow-up assessments lasting approximately 25-30 minutes that mirror baseline measures at 3-, 6-, and 12-months. Participants are remunerated ($40 at baseline, $40 at 3-months, $45 at 6-months, and $50 at 12-months) in cash or gift card (e.g., Amazon). Follow-ups are primarily online, without staff interaction, however, in the event a participant elects in-person follow-up staff administering assessments are blinded to condition assignment.

2.5 RCT Intervention Conditions.

2.5.1. Health coach session: Consistent with a telemedicine hub model, research assistants connect participants to the remote health coach using a telehealth platform such as Facetime or Zoom. Health coaches are bachelor's-level or higher staff hired who have relevant backgrounds and experience in fields such as social work, psychology, counseling. Health coaches are further trained in MI and CBT strategies by the study team and supervised weekly by experienced master's-level coordinators and doctoral-level investigators. Weekly supervision includes reviewing audio recordings of BI sessions and portal transcripts. The ~45 minute session (Table 1) blends elements of efficacious

brief motivational interventions from our prior work, including an opioid-focused brief intervention[19] and developmentally appropriate content for ages 16-30 based on our prior alcohol-focused brief interventions.[22,34,35] The intervention guide is housed in an internal website that is only accessible to study staff and includes decision-support screens to guide intervention delivery and enhance fidelity (e.g., help screens, reminders to use readiness rulers), allowing health coaches to collect within session para-data (e.g., strengths), consistent with prior work that found para-data are associated with important MI mechanisms and clinical outcomes.[36–38] Our session, outlined in Table 1 is rooted in the *Why Change* (e.g., benefits/reasons) and *How Change* (e.g., strategies) model of MI.[39,40]

The remote health coach session uses MI strategies to engage and explore individuals' situations, allowing for in-the-moment tailoring to address needs relevant for AYAs using MI concepts (e.g., supporting autonomy, acceptance, collaboration, evocation). During *Why Change*, health coaches review and affirm participants' goals and strengths, and invite discussion of opioid misuse as well as other substance use. MI skills (open questions, affirmations, reflections, summaries), seeking permission, Elicit-Provide-Elicit, elaboration, rulers, and autonomy support are used. Elicit-Provide-Elicit is a tool for collaborative psychoeducation used to explore risk perceptions of opioid medications and/or overdose in a highly tailored manner (based on what the participant knows/says).[41] Personally-specific benefits of change are elicited and reinforced; as many young people may be pre-contemplative about change, health coaches learn to elicit hypothetical benefits of future change or scenarios for choosing to avoid use (e.g., important family function, work, driving). After summarizing change talk, health coaches explore *How Change*, eliciting personally tailored tools to address misuse of substances and risk factors. Tools include brainstorming alternatives to address motives and risks (e.g., pain and sleep, coping, diversion refusal, overdose, safe driving, leisure/social fun). If applicable, participants are encouraged to consult their primary care or other medical providers with questions. Health coaches elicit how participants manage challenges to build self-efficacy based on prior success and explore barriers, and use rulers to elicit confidence and commitment to change by elaborating change talk. The health coaches close with a strategic summary, eliciting a next step toward goals. Health coaches review tailored resources, such as obtaining naloxone, and encourage disposal of leftover medications with the provided pill disposal bags.

2.5.2. Portal: We developed a web-based portal with manualized content for future implementation into existing means of patient communication (e.g., portals, texting, e-mail). The portal resides on internal research servers in the Michigan Medicine network and is only accessible to study staff (via secure log-in) and enrolled participants who have created personalized passwords. Health coaches push a portal message about twice weekly using MI strategies to engage participants in a dialogue around developmentally tailored and personally relevant topics (e.g., opioid use, motives, risk factors) consistent with the Why and How model of MI[39,40] (Table 2). Messages include similar components (e.g., responding to prior patient replies, introducing new content, eliciting response, and providing resources, including encouraging use of the disposal bag) varied throughout the 30-day messaging period. Messages are tailored using baseline data (e.g., opioid use/misuse,

motives, depression, binge drinking, other drug use). For those receiving the health coach session, coaches review a progress note from the session for further tailoring messages (e.g., goals, one next step, tools, etc.). Messages are further tailored to AYA responses, as done in-the-moment during face-to-face therapy. For example, messages about tools are tailored for an individual who reports clinically significant depression symptoms at baseline (e.g., behavioral activation), whereas those who report no depression may receive tools related to general stress reduction coping skills (e.g., physical exercise, social support, etc.). Also, messages about substance use are tailored, for example, focusing on benefits of avoiding concurrent use of alcohol/opioids for those who drink and overdose response for those with more severe misuse. Although participants may not respond to every message sent, simply viewing a message could contribute to behavior change. Further, token gifts (e.g., stress ball, ice pack, notebook) displaying the portal name are sent as a participation reminder during the 30-day period, but are not a contingency of participation. When participants do not reply to an initial message, health coaches send follow-up messages in the portal with reminders sent via other modalities (e.g., text, email, private message on social media handles provided by participants) or a telephone call. In addition, health coaches respond to participants' replies in an MI manner to elaborate the conversation and elicit and reinforce change talk, minimize sustain talk, and plan. The participant-facing portal provides a crisis text/phone line for immediate help (e.g., for participants experiencing acute suicidal ideation) and link to online resources.

2.5.3. Enhanced Usual Care (EUC) Control Condition.—

Given the lack of opioid-focused screening and prevention interventions or early interventions for AYAs in the ED setting, we chose an EUC as a control condition to offer a minimal resources. The EUC condition involves reviewing a community resource brochure, exceeding the ED's current standard of care, at the intake (e.g., in person in the ED; remotely mailed/e-mailed). For post-intake EUC, we send the community resource brochure to participants by email. The resources include information on topics such as: storage/disposal, overdose prevention, naloxone, suicide hotlines, mental health, and substance use treatment. Although pregnant women are excluded at baseline, enrolled participants may become pregnant during the study, so risks of opioid/other substance use during pregnancy are included in this resource brochure. The EUC resource brochure is additionally shared with all participants at enrollment and in the form of a pdf included with each follow-up survey invitation, regardless of condition, to control for any effects of exposure across conditions. Further, as part of EUC, all participants receive an opioid disposal bag when enrolling, either in-person or mailed.

2.6 Anticipated Participant Demographics

Our targeted enrollment is N = 1170 AYAs ages 16 to 30 and is expected to reflect the characteristics of the patient population at the ED. Based on prior studies at the study ED, we estimated that biological sex of the sample would be ~55% female and 45% male. In our pilot above, 78% were female sex (69% identified as female gender). With regard to race, we anticipate ~79% White, ~9% Black/African American and the remaining individuals from multiracial and other racial identities with ~6% identifying as Latinx. In our pilot, we saw greater proportions of Black/African Americans (15.4%) with 77% White and 7.7% from

other backgrounds; but 15.4% identified as Latinx. The mean age in our pilot was 22.9 years (*SD* = 4.5). It is important to note that the pilot took place during the initial surge of COVID-19 and thus is may not be representative of usual ED conditions and the patient population. For example, prior work has documented that ED volume decreased during this initial surge and that reasons for ED visits have shifted.[42]

2.7 Measures

The trial is part of a cooperative (HEAL Prevention Cooperative: HPC) along with several other studies funded through the NIH HEAL Initiative. As part of the HPC, investigators from each site agreed to use several common measures across trials. As such, several measures were adapted to meet unique needs of the HPC studies and will be cited herein as "HPC" when significant modifications were made for use by the HPC. Measures of outcome are repeated across screening/baseline and follow-up assessments. Below, we focus on our pre-registered primary and secondary outcomes, however, our assessments also include a number of other measures of potential mediators and moderators, and other exploratory outcomes.

2.7.1. RCT eligibility screening: The screening survey is self-administered and contains a number of items to assess trial eligibility and stratification variables as well as selected demographics, consistent with the HPC. Trial eligibility involve: a) past 12-month prescription or illicit opioid misuse, *or* b) past 12-month prescription opioid use plus at least one other risk factor. The specific risk factors are: other drug use or misuse of prescription sedatives or stimulants in the past 3 months; binge drinking in the past 3 months; positive 2-week depression screening; past-year suicide attempt; or past 2-week suicidal ideation. Items assessing opioid use and misuse (e.g., *"without a doctor's prescription or differently than how a doctor or medical provider told you to use it"*) are based on definitions from the HPC, with response options based on the National Epidemiological Survey of Alcohol and Related Conditions (NESARC) capturing frequency on a 12-point scale from "Never" to "More than Once a Day."[43] Other drugs queried are: cannabis, cocaine, methamphetamine, and hallucinogens, with a similar 3-month frequency response scale ("Never" to "More than Once a Day"). Misuse of prescription sedatives and stimulants use the same 3-month response scale, with misuse defined consistent with the HPC-provided wording above. Binge drinking is assessed within the Alcohol Use Disorders Identification Test-Consumption[44], modified for a 3-month period and sex-specific binge levels (i.e., at least 4 standard drinks for women, at least 5 for men). We use the Patient Health Questionnaire-2 (PHQ-2) to screen for past 2-week depression symptoms.[45,46] Recent (past 2-week) suicide ideation is captured using an item within a self-reported Columbia-Suicide Severity Rating Scale (C-SSRS) severity of ideation subscale, with a single item assessing past-year suicide attempts adapted from the C-SSRS behavior scale.[47,48]

In addition, to screen for exclusion criteria (severe opioid use disorder risk) and to determine opioid risk stratification, we measure 3-month misuse of both prescription and illicit opioids per the HPC definitions combined with the NIDA-Modified ASSIST (Alcohol Smoking and Substance Involvement Screening Tests).[29–32] Individuals with scores of 27+ on either ASSIST subscale are excluded and we also exclude individuals who report injection drug

use on the ASSIST item. Prior to approach ED patients who are presenting for pregnancy or related reasons or cancer are excluded from recruitment; however, we also query pregnancy status[49] and cancer status[50], to assess these exclusion criteria.

2.7.2. Primary outcomes.—The modified ASSIST for prescription opioids and street opioids used at screening is repeated at all follow-ups to assess our primary outcomes at 3, 6-, and 12-months via total scores. The ASSIST has been validated for computer self-administration;[51] it is reliable (test-retest reliability kappas = 0.58-0.90)[30] and valid.[52,53]

2.7.3. Secondary outcomes.—There are 5 secondary outcomes measured at baseline and follow-ups. 1) Items based on the Addiction Severity Index (ASI) measure past 30-day opioid consumption.[54–56] 2) Overdose risk behaviors (e.g., co-use with alcohol/sedatives, route of administration, etc.) are assessed as done in prior work[19] using a 3-month recall period. 3) Other drug (see eligibility section) and alcohol consumption are queried using past 3-month frequency items with response options based on the NESARC ("Never" to "More than Once a Day"). 4) Substance use consequences are measured with items from prior scales and the HPC that assess a range of past 3-month consequences due to opioids, alcohol, and/or cannabis use.[19,57–60] 5) Five items regarding impaired driving were adapted from the Young Adult Driving Questionnaire for use in this trial.[61]

2.8 Planned analyses

We will compare the effects of the health coach session+EUC, EUC+portal, and combination of the health coach session+portal interventions to EUC+EUC on the primary outcome of opioid misuse severity over time (baseline, 3-, 6-, and 12-months) for four measurements in longitudinal analyses. Additionally, we will examine the comparative effectiveness of the interventions. Generalized linear mixed models (GLMM[62]), also known as random effects or growth curve models, will be used to analyze the longitudinal data with a log link. GLMMs use all available measurements, allowing subjects to have an unequal number of observations and producing unbiased parameter estimates as long as unobserved values are missing completely at random (MCAR) or missing at random (MAR). The model will include fixed effects for the effects of health coach session and portal and the interaction between health coach session and portal. Additionally, the model will include a fixed effect for time point and interactions between time points and each main effect and interaction term of the interventions. With this model, we will be able to assess the main effects of the health coach session and portal and the interaction effect of health coach session x portal at each time point. We are primarily interested in the pairwise comparisons of treatment combinations. The GLMM will also include random effects for the intercept and time and an unstructured within-person correlation structure for the residual errors and will adjust for age and sex. Model diagnostics will be used to determine suitability of more parsimonious (e.g., autoregressive) correlation structures, and nonlinear (e.g., quadratic) effects for time. Additionally, we will assess the fit under the Poisson distribution assumption using the scaled Pearson statistic and compare to the fit of the over-dispersed (generalized) Poisson, negative binomial, zero-inflated Poisson, and/or zero-inflated binomial models by log likelihood values.

Secondary analyses examining efficacy on other outcomes will be modeled similar to above. The Poisson distribution will be checked for these outcomes where appropriate whereas the identity link will be used for continuous outcomes and the logit link for binary outcomes. In addition, we will examine baseline (e.g., sex, age, opioid risk severity) and time-varying factors (e.g., self-efficacy) that predict outcomes. To investigate moderation, interactions between the moderators of interest and main effects of the treatment variable will be assessed in the models specified above. To investigate mediation, we will establish the three preconditions for mediation derived from Baron and Kenny's causal steps approach. We will examine the mediators in structural equation models using the R package lavaan to determine indirect effects using bootstrapping. Bootstrapping does not assume normality of the product term used to examine indirect effects. Our mediation hypotheses are not time-specific, so we will compute and report all indirect pathways and their respective effect size coefficients. The reported path coefficients are completely standardized. The reported overall total effect, overall direct effect and overall indirect effect coefficients are unstandardized. We will use the proposed cut-off criteria to assess the fit between hypothesized models and the data: CFI>0.95, RMSEA<0.06, SRMR<0.08. The lavaan package is able to use full information maximum likelihood estimation to efficiently address any missing data that is either missing completely at random or missing at random in any of these constructs.

2.8.1. Power analysis and sample size—Power and sample size was estimated based on prior work from our team[19,24], the brief intervention literature[22,63–66], and initial pilot data which showed lower opioid misuse base rates than prior work, although effect sizes from pilot studies can have large standard errors and be unstable).[67] Sample size for this study is based on the primary aim, with opioid misuse score as the primary outcome. We are powered for our primary aim to compare each of the three intervention groups to EUC+EUC and to each other. Power was estimated based on $N = 1,170$ and an 85% follow up rate (estimated final $N = 994$, or 248/group) which does not consider imputations and other strategies for handling missing data without reducing sample size. We estimated power assuming a simpler model with one follow-up, a Poisson distribution of the primary outcome, and computed sample size by simulation using R 3.5.1. Conservatively, we used a Bonferroni correction for 6 pairwise treatment comparisons, setting the type I error at 0.008. Then, with 248 participants/group, we maintain 90% power to detect a rate ratio of 0.8^{19} if the base rate is as low as 2.8; if the base rate is as low as 1.5, we have 90% power to detect a rate ratio of 0.73. These effect sizes are modest, however, the interventions are scalable and thus could have high impact.

3. SUMMARY

3.1 Overview of Study

This RCT is testing the efficacy of early interventions to prevent/reduce opioid misuse and opioid use disorder using a 2 x 2 factorial RCT design involving combinations of first- and second-stage strategies. Specifically, participants are effectively randomized at intake to one of four arms: 1) health coach session + portal, 2) health coach session + EUC at 30 days, 3) EUC at intake + portal, and 4) EUC at intake + EUC at 30 days. The primary outcome is opioid misuse, and secondary outcomes are other opioid outcomes (e.g., days of opioid

misuse, overdose risk behaviors), and other substance misuse and consequences. Findings will identify efficacious and parsimonious interventions to prevent/reduce opioid misuse, while also estimating costs of implementation.

3.2 Importance of Scalable Opioid Prevention Interventions

Scalable, developmentally-tailored efficacious strategies are needed to not only prevent misuse among those using opioids, especially those with other risks associated with adverse outcomes, but also to prevent transition to opioid use disorder. If our interventions are deemed efficacious, this RCT will provide such scalable early interventions for health systems using technology infrastructure that already exists. For example, in response to the COVID-19 pandemic telehealth is now more common to health systems than ever before[68–71], meaning there is now infrastructure in many health systems to deliver such telemedicine driven to ED patients. Further, patient portals are being used throughout health systems in a variety of ways[72], but have not yet been tapped for their potential to deliver behavioral health interventions. The 24/7 access to patient portals is an advantage because participants can interact when they choose to in their busy lives from a variety of locations. Moreover, these interventions also provide a flexible working model for staff, who could be located in the ED, in a separate telemedicine hub, or at home. For example, in the context of our pilot work conducted early during the COVID-19 pandemic, interventions occurred remotely from health coaches to patients' in their homes after the ED visit, an even more flexible model. Our interventions are also consistent with continuing care approaches[73] which facilitate linkage to other healthcare settings. Harnessing technology for resource-light delivery could therefore maximize translation of these secondary prevention efforts into routine clinical care, with high impact on AYAs' trajectories of health and well-being.

3.3. Novel Aspects of the Design

This study has several innovative elements. Although single-session brief motivational interventions are not uniquely novel, the application to opioid misuse and our delivery approach increase innovation by harnessing technology, which is appealing to AYAs, to facilitate remote video delivery by a health coach in a tele-medicine hub, promoting fidelity using an online clinician support toolkit to structure the session while allowing personalization. Online support toolkits such as ours allow for within session data capture potentially identifying active ingredients of interventions.[35–37] Further, extending intervention delivery post-discharge and capitalizing on young peoples' use of technology, our portal messaging is novel, and, with the rise of patient portals in health systems, this feature enhances future ED implementation and extension of interventions into AYAs' day-to-day lives. The portal content is flexible to allow for real-time tailoring to prevent/reduce misuse, addressing heterogeneity in motives (e.g., pain management, coping) and other risk factors (e.g., depression, other substance use). Use of the fully-crossed 4-group RCT design will help identify the optimal combination of interventions based on risk severity in terms of efficacy, cost-effectiveness, and reimbursement mechanisms. Our conceptual model, which guides the examination of moderators (e.g., sex, motives) and mediators (e.g., self-efficacy) of efficacy, will provide unique information regarding mechanisms of behavior change and identify opioid-related risks to inform translation. The final product of these strategies

involves an online toolkit adapted for our interventions to include one-stop shopping for screening, a health coach support guide, and training videos to increase scalability, with cost analyses guiding future implementation.

3.4 Limitations

In designing this trial, we carefully weighed the advantages and disadvantages of scientific protocol decisions and there are, of course, limitations in the current approach. First, the trial results may have limited generalizability to other ED settings since our study takes place in a single site (e.g., not representative of an urban ED, not representative of smaller community hospitals). Further, conducting a trial during a historical public health event like COVID-19 has potential implications for generalizability to future populations. Additionally, to advance the science on opioid prevention in AYAs, there was a requirement to harmonize measurement across HPC studies to address larger scientific questions about the progression of opioid misuse. This greater harmonization effort required modifications to measures, potentially impacting reliability and validity. The use of an external portal platform as opposed to the health system's EHR-integrated patient portal could be viewed as a limitation; however, because of the need to maintain confidentiality pertaining to *research participation* specifically we found it necessary to build a separate portal. Finally, we note that the use of health coaches of varying skill levels at the bachelor's and master's level (as opposed to master's-level licensed clinicians) could be a potential limitation because of the limited clinical experience of some of these staff. Nonetheless we note that our coaches met fidelity thresholds in our pilot and that a number of studies have used peers and lay health workers without extensive clinical experience to deliver MI meeting a number of fidelity thresholds.[74–76] Further, as Miller and Rollnick[41] recommend we use ongoing quality assurance and fidelity monitoring in this trial.

4.0 Conclusions

This paper describes the protocol for a RCT testing the efficacy of behavioral interventions to prevent escalation of opioid misuse among AYAs with prior opioid use or misuse. Planned dissemination activities are aligned the larger Heal Prevention Cooperative efforts and will include reporting of trial results within one year of study completion on ClinicalTrials.gov. The work is innovative by testing the interventions required to maximize effects on reducing the primary outcome of opioid misuse severity, as well as secondary outcomes of other opioid outcomes (e.g., overdose risk behaviors) and other substance use, while identifying costs to inform implementation. In light of the current opioid crisis, this study will have high impact by testing scalable intervention approaches delivered by health coach, allowing for real-time tailoring and personalization based on motives and risk severity. Content is easily adapted over time and with remote delivery and integration into patient portals enhancing scalability and efficiency (during the COVID-19 era and beyond) while being responsive to the evolving opioid crisis.

Acknowledgements:

This research was supported by the National Institutes of Health through the NIH HEAL Initiative under award number UG3/UH3 DA050173. The content is solely the responsibility of the authors and does not necessarily

represent the official views of the National Institutes of Health or its NIH HEAL Initiative. Drs. Bonar and Walton and Ms. Kotov wrote initial drafts of this paper; however, all authors have contributed to the writing and editing this manuscript and approve the final manuscript.

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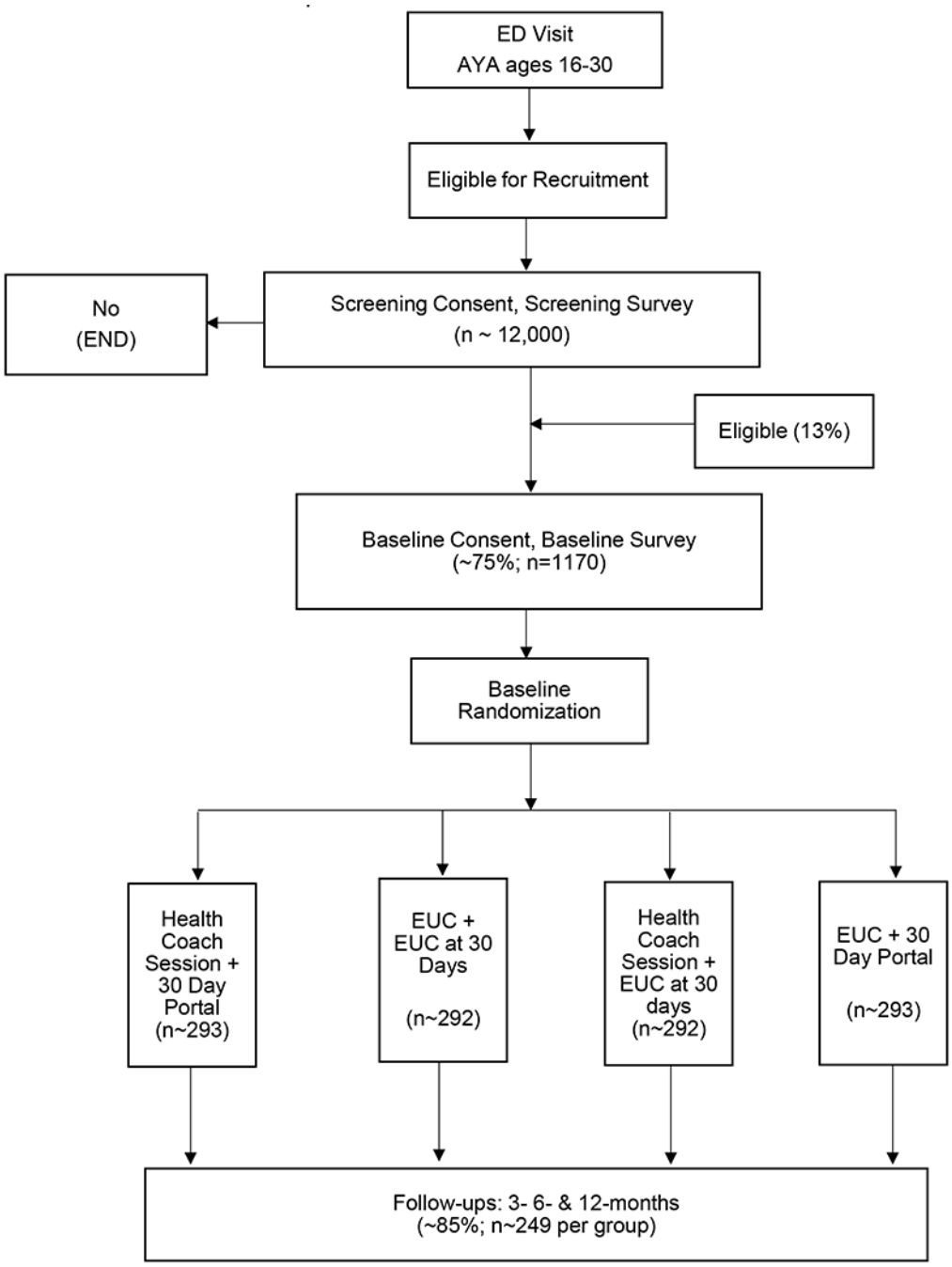

Figure 1.

Flow Chart for Randomized Control Trial Comparing Four Intervention Groups Aiming to Prevent and Reduce Opioid Misuse

	Enrollment	Allocation	Post-Allocation				Close Out
	Baseline		30 Days	3 Months	6 Months	12 Months	
Enrollment							
Screening Consent	X						
Eligibility Screen	X						
RCT Consent	X						
Baseline Survey	X						
Allocation		X					
Conditions							
Intake EUC		X					
Health Coach Session		X					
Portal		X	X				
Post-Intake EUC			X				
Key Outcome Variables Assessments							
ASSIST	X			X	X	X	
Opioid Consumption	X			X	X	X	
Overdose Risk Behaviors	X			X	X	X	
Other Drug and Alcohol Consumption	X			X	X	X	
Substance Use Consequences	X			X	X	X	
Impaired Driving	X			X	X	X	

Figure 2.

SPIRIT Diagram for Randomized Control Trial Comparing Four Intervention Groups Aiming to Prevent and Reduce Opioid Misuse

Table 1.

Health coach session components

Why Change?	
Agenda Setting	• aReview session purpose, answer participants' questions, emphasize autonomy, build rapport, seek collaboration/ permission
Strengths, Goals	• Elicit/affirm AYAs' goals and values (e.g., health, relationships, daily life) • Elicit/affirm strengths (e.g., reliable, humorous, problem-solver, etc.)
Substance Use	• Review opioid use & other drug use, motives/reasons for use (e.g., pain, coping, enhancement, social) and reasons to avoid use/misuse
Exploring Risk	• Elicit-Provide-Elicit for overdose signs/symptoms • Elicit concerns & skills for witnessed overdose (i.e., friend/family overdose)
Benefits of Change	• Elicit benefits of changing opioid/other substance use to reduce risks and address motives; benefits of alternative, non-substance use coping strategies • Reinforce and elaborate change talk, strategic summary of change talk
How Change?	
Scenarios	• Explore risky situations for misuse (e.g., pain, coping, social settings, overdose/driving), including mental health concerns • Identify tools to reduce risk and alternatives to address motives, including mental health coping, elaborating change talk
Summary & Plan	• Strategic summary eliciting one next step toward change/goals • Tailored review of community resources (e.g., naloxone, opioid disposal, mental health, etc.)

Table 2.

Sample Portal Message Topics

• **Starting the conversation** (e.g., rapport building rapport and engagement)
• **Pain management** (e.g., tools/strategies, prevention, referral, avoiding opioids)
• **Mental health** (e.g., coping with anxiety, depression, stress, suicidality, daily struggles, social support)
• **Physical health and sleep** (e.g., substances effects on sleep/health, tools and strategies, coping)
• **Lifestyle and leisure** (e.g., supporting goals and planning, developing discrepancy, substance-free positive leisure, substances and social settings)
• **Substance use** (benefits of harm reduction or change, tools for risky situations, managing triggers)
• **Wrapping up** (e.g., reminder of end of portal period, summary, planning and next steps, referrals and resources)