Official Title: Delivering Patient-Centered Adolescent Preventative Care with Training and Technology

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1. Background and Rationale

Adolescents have some of the highest rates of risk behaviors of all age groups and health behaviors developed in adolescence can persist into adulthood. Health risk behaviors, such as alcohol and other drug use, smoking, unsafe sexual activity, and poor nutrition and physical inactivity are among the most common causes of adolescent illness and premature death. These behaviors carry significant risks for subsequent disease, disability, and healthcare burden. Despite these risks, health risk screening in primary care is infrequently performed and results are rarely followed by targeted intervention.

Studies have shown that electronic health risk screening is feasible and efficient in clinical practice, increases adolescents' comfort with disclosure of behavior and encourages utilization of preventive health services. Based on this evidence, electronic multi-risk behavior screening tools are being developed for adolescent care settings. However, to reduce risk behaviors, screening needs to be linked to interventions. In response to the need for screening-linked interventions, our study team has developed a web-based, electronic screening and Personalized Motivational Feedback tool which we refer to as the "Check Yourself" app. Based on motivational interviewing, a technique to mobilize personal change, Check Yourself is designed to promote healthy choices for the multiple behaviors relevant to adolescents. Building on electronic health interventions, primary care providers (PCPs) can play an essential role in helping adolescents to make healthy behavior choices.

Adolescents list PCPs among the first people with whom they would consider discussing risk behaviors, and report greater satisfaction with care when PCPs discuss these sensitive topics with them. Thus, primary care visits present a key opportunity for improving the health of adolescents. However, to take advantage of this opportunity, health systems strategies are needed that can practically be implemented in the time-pressured environment of primary care. Emerging evidence suggests that the consistency of preventive counseling can be increased through provider training and the provision of screening tools; yet, we know very little about the quality of such counseling, and if it impacts outcomes that are important to adolescent patients themselves.

In order to address these gaps, this proposal aims to test an interactive adolescent-centered PCP training (I-ACT) to increase PCPs' ability to engage and empower adolescents to make healthy behavioral choices and to stimulate patient-provider discussions around health behavior choices. We will examine the impact of our training in the presence of Check Yourself, which systematizes screening, delivers motivational feedback directly to adolescents, and generates a targeted report to PCPs summarizing youth risk behaviors and recommendations for next steps in care.

1.1. Purpose

The purpose of this study is to evaluate the perceived impact and effectiveness of our system of interventions (I-ACT with Check Yourself) among a sample of adolescents aged 13-18 drawn

from the targeted primary care clinics using a group who receives usual care as a comparison. This study has two aims:

Aim 1. To evaluate I-ACT with Check Yourself on intermediary targets: improving adolescent motivation for health, increased provision of appropriate preventive counseling, and follow-up care. We will examine the impact of I-ACT with Check Yourself on adolescent self-report of motivation for health at baseline and 3, 6 and 12 months following the primary care visit. We will also examine the impact of I-ACT with Check Yourself on the adolescent self-report of receipt of PCP-delivered risk reduction counseling at one day following the primary care visit and follow-up care at 3, 6 and 12 months following the primary care visit.

Aim 2. To evaluate the effects of I-ACT with Check Yourself on adolescent satisfaction with the provider visit, perception of patient-centeredness of care, and health risk behaviors. We will explore the impact of I-ACT with Check Yourself on health care satisfaction among adolescents and caregivers at one day following the primary care visit. We will also explore the impact of I-ACT with Check Yourself on adolescent self-report of their perception of patient-centeredness of care at one day following the primary care visit. We will examine the effect of I-ACT with Check Yourself on producing significantly lower rates of alcohol use, marijuana use, unprotected sexual activity, and depression compared to a usual care group at baseline and 3, 6, and 12 months after the primary care visit. We will also examine the effect of I-ACT with Check Yourself on producing significantly higher levels of physical activity, fruit and vegetable consumption, and seatbelt and helmet use when compared to a control group at baseline and 3, 6 and 12 months after the primary care visit.

2. Criteria for Subject Selection

2.1. Sample Size

We plan to enroll approximately 300 adolescent (age 13-18) and parent dyads who have an appointment with a participating provider affiliated with one of six participating practices in the Puget Sound Pediatric Research Network (PSPRN). We also plan to enroll approximately 30 PSPRN providers (about 5 providers per clinic).

2. Gender of Subjects

This study does not have any gender-based restrictions. However, given that women are more frequently primary caregivers and PCPs, we estimate the following gender distribution in our study population:

Adolescents: 150 Females and 150 Males
Caregivers: 240 Females and 60 Males
PCPs: 18 Females and 12 Males

3. Age of Subjects

Participants will include adult *caregivers and PCPs* (over the age of 18 years) and *adolescents* (age 13-18). As health risk behaviors typically begin in adolescence and persist into adulthood, we are targeting adolescents rather than children less than 13 years of age.

4. Racial and Ethnic Distribution

The proposed study population will include a wide cross section of adolescent patients and their caregivers, including many families of ethnoracial minority status. We will monitor diversity in our sample throughout the course of recruitment and adapt recruitment efforts as needed to assure a representative sample. The Central Puget Sound geographic area, where our study population is situated, consists of the following approximate ethnic and racial breakdown:

73% White
5% African American
12% Asian, Hawaiian or Other Pacific Islander
1% American Indian or Alaska Native
9% some other race (alone) or two or more races

In addition, 9% of individuals in this geographic area are of Hispanic or Latino ethnic background.

5. Inclusion Criteria

Eligible caregivers will have a child 13 to 18 years old who has an appointment with a participating provider at a PSPRN clinic and will be able to understand English.

Eligible adolescents will be 13 to 18 years old, have an appointment with a participating provider at a PSPRN clinic and will be able to understand English.

Eligible PCPs will include providers (i.e., pediatricians, family practitioners, physician assistants and nurse practitioners) affiliated with a PSPRN clinic who are following a panel of adolescent patients and will be able to understand English.

6. Exclusion Criteria

Caregivers will be excluded from the study if they do not speak English; or if their child is not eligible or declines to participate in the study.

Adolescents will be excluded from the study if they do not meet age requirements, do not have an appointment with a participating provider at a PSPRN clinic, lack the means to complete follow-up interviews (i.e., have neither telephone nor internet access), have a sibling who has been/is being enrolled in the study or have previously participated in our previous trial comparing Check Yourself to usual care, and/or are not able to understand English. Our experience in the Seattle region is that due to excellent English Language Learning school supports, inability to read or understand English is a barrier for <0.5% of adolescents. Thus, we do not anticipate that language restrictions will significantly limit the demographic distribution of our participants.

PCPs will be excluded from the study if they do not speak English, are not following a panel of adolescent patients, and are not affiliated with a participating PSPRN clinic.

7. Vulnerable Subjects

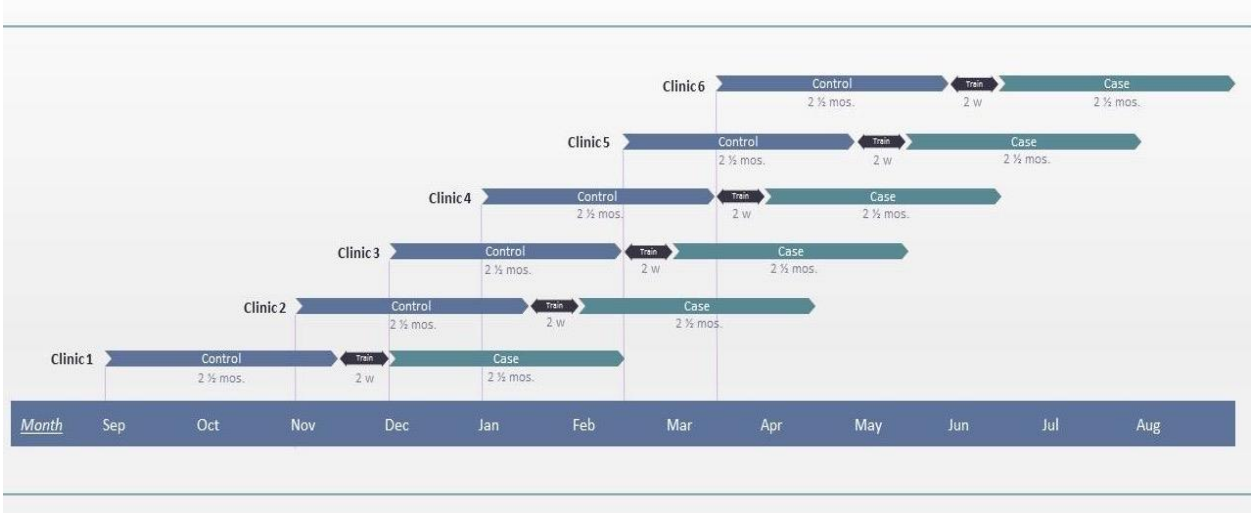
This study's focus is on adolescent health care, and adolescents are study participants. We plan to enroll 300 adolescent subjects aged 13-18. Most will be minors. Study activities for minor adolescents will be no different from study activities for 18-year-old adolescents. The risk/benefit ratio is the same for all adolescent participants regardless of age. Research staff will obtain oral consent from 18-year-old participants directly, without contacting a caregiver. For younger adolescents, research staff will first obtain oral parental consent before obtaining oral assent.

3. Methods and Procedures

3.1. Study Design

This study will evaluate the effect of I-ACT with Check Yourself on adolescent-perceived quality of care (i.e., satisfaction and perception of PCP communication), motivation for health, and health risk behaviors using a stepped wedge study design. The study will take place in 6 participating PSPRN affiliated clinics, where the system of interventions (I-ACT with Check Yourself) will be rolled-out sequentially to the clinics, chosen in random order, over spaced time intervals (see Figure 1). We refer to pre-implementation of I-ACT with Check Yourself, as the control period and post-implementation as the intervention (i.e., case) period.

Figure 1: Stepped Wedge Study Design and Timeline



We anticipate that approximately 30% of youth approached will participate in the study. Thus, we will invite approximately 1000 adolescent/caregiver dyads to participate in the study, in order to yield 300 adolescent/caregiver dyad participants in our total sample. Upon enrollment, caregiver participants will be asked to complete a brief (10-minute) web-based questionnaire about their education/occupation, their adolescent's health history, and an open-ended question about what they would like to get from PCPs for themselves and their adolescent. Adolescents who enroll in the study will receive either electronic health screening alone (i.e., control group) if

their clinic appointment occurs in the pre-I-ACT implementation period or Check Yourself (i.e., intervention group) if their clinic appointment occurs in the post-implementation period.

At baseline (T1), adolescents will be asked to complete a web-based screening survey that includes questions about guideline-recommended health risk behavior screening areas, including substance use, nutrition, physical activity, sexual behavior, depressive symptoms, and safety. The screener questions themselves are current standard of care. Adolescents will also be asked to report their age, gender, race/ethnicity, interest in discussing health risks with the PCP, and self-efficacy.

Adolescents in the control group will complete the web-based screening survey for research purposes, but neither they nor their PCP will receive feedback about their health behaviors. PCPs will screen and counsel the patient as they would normally do under usual care conditions, consistent with the current standard of care.

During the intervention period, participating PCPs will receive adolescent-centered communication training, based on the tenets of motivational interviewing, to reinforce healthy behavior choices and to engage youth and parents to reduce risk behaviors as appropriate. PCPs will also receive three feedback reports (baseline, 2 months and 4 months) on adolescent-reported receipt of counseling on each of the target behaviors and adolescent-reported visit satisfaction and follow-up care. PCPs will not be asked to complete any study questionnaires; all of the outcome data will be gathered directly from adolescents and caregivers. Outcome data for the three feedback reports will be given to providers in aggregate form and will be void of individual identifiers.

Adolescents in the intervention group will receive full personalized motivational feedback following completion of the screening survey, both with web-based delivery. Their PCPs will receive a summary report which will include specific information on the adolescent's responses that will allow them to reinforce healthy behavior choices and implement further brief, in-person interventions for moderate to high risk adolescents. The personalized feedback to the participant and provider is consistent with current standard of care. However, the electronic method of delivery is unique to this project.

In order to administer follow-up surveys, we will ask adolescents to provide an email address, cell phone number, or phone number. One day (T2) following their PCP appointment, adolescent participants will be asked via email, text message or phone to complete a survey about their motivation for health, perception of PCP communication, and experiences. Both adolescents and their caregivers will be asked about their satisfaction with treatment during the appointment with their PCP. In addition, caregivers will be asked open-ended questions to assess the provider's delivery of caregiver education regarding strategies to reduce health risks for their child during the visit.

Three (T3), six (T4) and twelve (T5) months following their PCP appointment, adolescent participants will be asked via email, text message or phone to complete all assessments

administered at T1 and T2 except the questionnaires related to delivery of preventive counseling, demographics, interest in discussing health risks with PCP, and self-efficacy. Additionally, adolescents will be asked about follow-up care they may have received. At T2 and T3, adolescent participants will be asked about their general satisfaction with their provider and will be asked 3-4 follow-up questions to ascertain satisfaction with the Check Yourself app and study. These surveys are not standard of care, because they are not collected as part of an appointment; however, the probability and magnitude of discomfort associated with the completion of these surveys is no greater than ordinarily encountered in daily life or during the performance of routine psychological examinations/tests or medical care.

3.2. Measures by Construct and Time point

Tables 1 and 2 describe the study measures by construct.

Table 1: Measures used in the study, organized by construct and method.

Measures and Constructs	Time point
Moderators	
Gender, age, race, household composition, school, truancy, support, goals, interest in discussing health risks with provider	T1(A)
Number of visits with provider	T2(A)
Health Self-Efficacy	T1(A),T2 (A), T3(A), T4(A), T5(A)
Caregiver Concerns	
Guidelines for Adolescent Preventative Services Caregiver Questionnaire: adolescent health risk behavior concerns.	T1(C)
Perception of provider engagement with the caregiver	T2 (C)
Intermediary Targets	
Health Motivation (Readiness to Change Rulers): Self-report used to assess adolescent motivation for change among specific health behaviors.	T1(A),T2 (A), T3(A), T4(A), T5(A)
Adolescent Report of the Visit: adolescent-report of the PCPs' delivery of risk behavior screening and counseling based on risk level.	T2 (A)
Interval Receipt of Care: adolescent self-report of extent of follow up care.	T3 (A), T4(A), T5(A)
Main Outcomes: Satisfaction & Perception of PCP Communication	

Satisfaction Questionnaire: self-report of satisfaction with care based on items adapted from the Consumer Assessment of Healthcare Providers and Systems (CAHPS) measure.	T2(A/C)
Adolescent Perception of Patient-Centeredness: adolescent self-report of how adolescents feel about visits with their primary caregiver.	T2(A)
Main Outcomes: Health Risk Dimensions*	
Alcohol Consumption and Marijuana Use: self-report based on items about typical quantity and frequency of drinking, smoking/using tobacco, and marijuana use (each calculated separately) over the past 30 days.	T1(A), T3(A), T4(A), T5(A)
Fruit and Vegetable Screener: self-report of fruit and vegetable consumption.	T1(A), T3(A), T4(A), T5(A)
Physical Activity Screener: self-report of physical activity.	T1(A), T3 (A), T4(A),T5(A)
Sexual Risk: self-report of sexual activity, birth control, and condom use.	T1(A), T3(A), T4(A), T5(A)
Patient Health Questionnaire-9 (PHQ-9): self-report of DSM-V symptoms for depression.	T1(A), T3(A), T4(A), T5(A)
Safety: self-report to assess behaviors that contribute to unintentional injuries (e.g., seat belt use, helmet use).	T1(A), T3(A), T4(A), T5(A)

Key: T1 = Timepoint 1 (Baseline) T4 = Timepoint 4 (6 month)
T2 = Timepoint 2 (1-day) T5 = Timepoint 5 (1 year)
T3 = Timepoint 3 (3-month)
A = Adolescent survey
C = Caregiver survey *See Table 2 for Individual Health Risk Outcomes and Summary Risk Variable

Table 2: Summary Risk Variable and Individual Health Risk Outcomes

TOPIC AREA	Original variable	Summary Health Risk Variable	Dichotomized Individualized Health Risk Variable (Risk vs. no risk)
EATING			
Sweetened beverage consumption	0, 1, 2, 3+	# of sweetened beverages consumed in a typical day	2-3+ vs 0-1
Fruit and vegetable consumption	0-5+	# of fruits and vegetables consumed in a typical day	0-3 vs. 4+/day
ACTIVITIES			

Physical activity (60+ minutes)	0-7	# of days with >60 minutes of physical activity in an average week	0-3 days/week vs. 4-7 days/week
Sleep	0-12+	# of hours of sleep on a typical night	0-7 hours vs. 8+ hours
SAFETY			
Seatbelt Use	4 pt. scale	Frequency of seatbelt use in a car	Not always vs. always
Helmet Use	4 pt. scale	Frequency of helmet use when bicycling	Not always vs. always
DUI/Riding with a DUI driver	Dichotomous	Yes vs. no	Yes vs. no
Texting while driving	4 pt. scale	Frequency of texting while driving (4-point scale)	NOT INCLUDED IN SUMMARY RISK VARIABLE
ALCOHOL AND DRUGS			
Drinking frequency	0-30	Decrease in # of days on continuous scale	≥1 (Ages 13-15) vs. 0 ≥2 (Ages 16-17) vs. 0-1 ≥3 (Age 18) vs. 0-2
Drinking quantity (typical or maximum)	0-15+	# of alcoholic drinks typically consumed per occasion	≥3 (Girls 13-17 and Boys 13) vs. 1-2 ≥4 (Girls 18 and Boys 14-15) vs. 0-3 ≥5 (Boys 16-18) vs. 0-4
Marijuana use frequency	0-30 days and/or 0-365 days	#of days used marijuana in the past 30 days and or year	≥1 days/month (Ages 13-15) vs. 0 ≥2 days/month (Ages 16-18) vs. 1 ≥1 days/year(Ages 13-15) vs. 0 ≥6 days/year (Ages 16-18) vs. 0-5
SEXUAL ACTIVITY			

Condom Use	4 point scale	Frequency of condom use with sexual intercourse	Not always vs. always (or not sexually active)
Birth control use	Dichotomous	Use of any birth control at last sexual intercourse (yes/no)	Not always vs. always (or not sexually active)
EMOTIONS			
Depression (PHQ-9)	0-27	Score on PHQ-9	Total score on PHQ 10 or higher vs. 0-9

3.3. Data Analysis and Data Monitoring

3.3.1 Strategies to Minimize Missing Data.

At the time of enrollment, we will gather the preferred and all available email addresses, phone numbers (including mobile for text messaging), and social networking inbox addresses for eligible adolescents. To confirm accuracy of the email address, participant payments will be sent electronically, via email, and participants will be instructed to contact study staff if payment is not received. We will also collect phone numbers for 3 friends or family members who would know how to reach the participant if we do not. Our experience is that we can maintain >85% of our enrollees over the course of the study. Despite our best efforts, we expect some attrition over the course of follow up, which has been factored into our sample size calculations. In the case that an adolescent does not have an email address, surveys will be completed by phone and payments will be sent via mail.

Maintaining statistical power is a key consideration. We will implement various recommended strategies for maximizing power within the current design, including use of covariates in data analyses when appropriate, preventing attrition and missing data, implementing advanced missing data analyses such as multiple imputation techniques using reliable measures, and maintaining integrity of the intervention throughout the study. For all analyses, we will start with models using all available data, not just complete cases. In addition we will apply inverse probability weighted methods to adjust for missing data and conduct sensitivity analyses looking at how other estimates are impacted by including the variables with missing values.

3.3.2 Data Analysis.

Data from the web-based surveys will be uploaded into STATA analytic software. Prior to analysis, all variables will be checked for validity, missingness, and distributional assumptions. Preliminary analyses required for variable construction, any required imputation of missing data, assessment of psychometric properties of scale scores, and assessment of the validity of study variables will be completed before analyses assessing

intervention effects. Data set documentation will then be developed and distributed to the study team. Before carrying out analyses addressing each of the research questions, an analysis plan will be formally presented to the study team and Project Advisory Board so a wide range of expertise and experience is brought to bear on each work product of the team.

Some key features of the stepped wedge design require special consideration in the planned analyses. First, the design involves unidirectional cross-over from the control arm to the intervention arm for all PCPs. This has to be captured by an indicator specific to PCP and time point. Second, there are natural hierarchical structures in the data with PCPs nested within clinics, patients nested within PCPs, and repeated assessments made within patients for some outcomes, such as health risk behaviors. Because different patient samples will be surveyed at each time point, within patient correlation over time should not be strong. Still, clustering at the clinic and PCP-levels needs to be examined in all analyses. Third, secular time trends need to be carefully examined and separated from the intervention effect. Based on these considerations, we will focus on model- based approaches (linear or generalized linear mixed effects models) for the main analyses, in addition to standard hypothesis testing techniques.

Aim 1 will compare intermediary targets at all clinics before and after the intervention using an analytic approach that both accounts for design features, repeated assessments within adolescents, time trends in these target behaviors during study period and adjust for potential confounders. For this aim we will use patients as the units of analysis. We will consider outcomes at the level of the patient (adolescent reported motivation for health and provision of appropriate preventive counseling).

Our primary analysis will be based on a set of mixed effects regression models. As an illustration, let's consider the adolescent self-reported health motivation (readiness to change, as other adolescent reported outcomes can be modelled in a similar fashion. Specifically, we will consider the following regression model:

$$Y_{ijk} = \mu + \alpha \boldsymbol{X_{ijk}} + \beta_k \boldsymbol{T_k} + \gamma_k \boldsymbol{X_{ijk}} * \boldsymbol{T_k} + b_i + b_{ij} + \varphi\ Covariates + \varepsilon_{ijk},$$

in which Y_{ijk} denotes the health motivation reported by *j*th patient within *i*th provider at *k*th time interval, $\boldsymbol{X_{ijk}}$ **is a binary indicator of exposure to the intervention for the provider and the predictor of interest**, T_k is a binary indicator of the *k*th assessment, b_i and b_{ij} are PCP and adolescent specific random effects that account for the within PCP and within adolescent correlations, and ε_{ijk} is the error term. Additional patient-level or PCP-level confounding variables can be adjusted in the model as well.

With this model, the fixed effects $\boldsymbol{\alpha}$ captures the treatment effects on mean responses and time-by-intervention interaction coefficients $\boldsymbol{\gamma_k}$'s captures the treatment effects across time. Fixed effects $\boldsymbol{\beta_k}$'s aim to capture any temporal trend or learning effects. Using this approach, both within-adolescents and between adolescents information will be used to estimate the treatment effects. All coefficients will be tested using Wald test. Also note this

model framework is flexible enough that a patient can be enrolled at any time during the study and the model can accommodate different numbers of post-intervention assessments. For example, for an adolescent enrolled after his/her PCP has received intervention, all X_{ijk}'s would take value 1 for that subject.

We will apply linear mixed effects models for Gaussian outcome Y_{ijk}, and generalized linear mixed effects models for other types of outcomes (e.g., logistic model for binary outcome).

For *Aim 2*, analyses will be based on patient survey responses to the 8-item satisfaction scale, patient perception of PCP communication, and the summary health risk variable, which will all be treated as continuous response variables. The summary health risk variable constructed from a count of dichotomized key risk behaviors (as shown in Table 2). First, satisfaction levels and risk behaviors will be summarized for each period (pre- and post-intervention) and will be compared using two sample t-tests. For the main analysis, we will apply mixed effects models similar to those proposed in Aim 1 to examine the intervention effect. For patient satisfaction, PCP satisfaction, adolescent's perception of PCP communication and health risk behaviors, the analysis will be cross-sectional comparisons at one day following the primary care visit. Let Y_{ij} denotes the satisfaction at one-day post visit of adolescent j within PCP I, let X_{ij} denote whether the PCP has received intervention at the time of visit, then the following mixed effects model can be applied

$$Y_{ij} = \mu + \alpha \boldsymbol{X_{ij}} + b_i + \varphi \, Covariates + \varepsilon_{ij},$$

where b_i accounts for within-PCP correlations for adolescents seen by the same PCP. The fixed effect **α** captures the intervention effect on the patient satisfaction. Similar model can be applied to PCP outcomes and we can account for within-clinic correlations as well.

When examining the intervention effects on adolescents individual risky behaviors (alcohol use, marijuana use, unprotected sexual activity, depression, physical activity, healthy food consumption, seatbelt and helmet use) at baseline, 3, 6, and 12 months after the primary care visit, same modeling framework as outlined for Aim 1 can be applied.

3.3.3 Heterogeneity of Treatment Effects.

The goal of any heterogeneity of treatment effects analyses will be to ascertain whether treatment effects vary significantly across subgroups of patients and to identify subgroups of patients that achieve the greatest benefit from part or entire treatment regimen. (PCORI Methodology Standard HT-1) Based on our current knowledge, we hypothesize that treatment effects may vary substantially across age groups (13-15 yrs vs. 16-19 yrs), gender groups (male vs. female), racial groups (White, African American, Asian/American Indian/Pacific Islander, and multi-racial), ethnic groups (Hispanic vs. non-Hispanic), adolescents with differential baseline motivation status (highly motivated adolescents vs. less motivated), and adolescents with differential self-efficacy (high vs. low) (PCORI Methodology Standard HT-2). We recognize the possibility that additional subgroups may

arise in the course of the analyses described above as we identify which factors modify the associations. (PCORI Methodology Standard HT-4) Our stepped wedge design allows us to employ both within participants and between participants information to estimate and compare treatment effects.

As we have outlined in the Statistical Analysis section, the primary analysis will be based on mixed-effects regression models in the following form, for example, when examining PCP outcomes (similar models will be applied to adolescent outcomes):

$$Yijk = \mu + \alpha Xijk + \beta k\ Tk + bi + bij + \gamma covariates + \varepsilon ijk,$$

in which Yijk denotes the appropriate preventive counseling rate for jth PCP within ith clinic at time interval k, Xijk is a binary indicator of exposure to the intervention (predictor of interest), Tk is a binary indicator of the kth assessment time interval, bi and bij are clinic and PCP specific random effects that account for the within clinic and within PCP correlations, εijk is the error term. Adjustment for additional clinic-level or PCP-level confounding variables can be incorporated into the model as well. With this model, the fixed effect α captures the treatment effect, while fixed effects βk's aim to capture any temporal trend. Using this approach, both within-PCP and between PCP information will be used to estimate the treatment effect.

Our treatment heterogeneity (TH) analysis will consist of two steps. The first step will be subgroup analysis, in which the above outlined regression models will be applied to each of the subgroups. We will then inspect the treatment effect sizes and significances across subgroup analyses to get a sense of the direction and magnitude of treatment heterogeneity. In second step we will formally test the treatment heterogeneity by including a treatment-by-group interaction term in the model:

$$Yijk = \mu + \alpha 1Xijk + \alpha 2Group + \alpha 3\ Xijk*Group + \beta k\ Tk + bi + bij + \gamma covariates + \varepsilon ijk,$$

A wald t-test on the coefficient α3 formally tests the significance of treatment heterogeneity across groups. (PCORI Methodology Standard HT-3) We may have to apply multiple comparisons adjustments to minimize false discovery rates due to large number of subgroup analyses.

Treatment heterogeneity can also be interpreted as effect modification, i.e., the treatment effects are being modified by group characteristics. However, such modifications may work through different mechanisms. For example, same intervention may be received differentially by different groups with one group embrace every aspect of the intervention and the other group does not comply at all. Or, different groups may respond differentially to the different treatment components, with one group respond better to one part of the intervention and another group to another part of intervention. Therefore, when examining treatment heterogeneity, we will have to apply careful scientific reasoning and scrutinizing, in addition to statistical analysis.

4.0 Data Monitoring and Management

The proposed research involves no greater than minimal risk to participants.

4.1 Adverse Events

Project staff will be trained to identify potential adverse events and instructed to report them immediately to Dr. Richardson or Dr. McCarty. Should any study participant or caregiver express concerns about the study or their participation or appear distressed during any study activities, the witnessing research team member will bring the matter to the attention of Dr. Richardson or McCarty, who will distinguish serious adverse events from non-serious adverse events. Serious adverse events will be documented and discussed with the IRB as soon as possible, and reported to the IRB within 48 hours. An annual report will be submitted to PCORI and the IRB summarizing all adverse events.

4.2 Data Quality Assurance and Confidentiality

Data quality assurance will be monitored on an ongoing basis by the Research Manager, Heather Spielvogle. She will each conduct routine protocol compliance checks to ensure that safety procedures, such as ensuring participant confidentiality and maintaining approved standards for data transport, are strictly adhered to at each site. All study data will be stored in password-protected computer files and identified with study IDs. Analytic data files will contain no identifying information. Other confidentiality issues are discussed in the prior section "Protection Against Risks."

4.3 HIPAA Compliance

All participants will be recruited from clinical sites, and as such their participation is subject to the Health Insurance Portability and Accountability Act of 1996 (HIPAA) privacy and security standards. All relevant staff has completed required HIPAA training and all research activities will be conducted in compliance with HIPAA standards. All study data will be securely stored and labeled as discussed on the "Data storage and confidentiality" section of this protocol, below. PCPs of participants assigned to the Check Yourself intervention will receive feedback including specific information on adolescents' responses that will allow them to reinforce healthy behavior choices and implement further brief in-person interventions for moderate to high risk adolescents. Although a participant's individual responses to the health screener constitute protected health information generated from the research study, since the results are shared with the participant's PCP for treatment and/or health monitoring purposes, this disclosure appears to fall within an exception of the minimally necessary requirement of the Privacy Rule (Section 164.502). PCPs will receive three feedback reports on adolescent-reported receipt of counseling on each of the target behaviors and adolescent-reported visit satisfaction and follow-up care gathered directly from adolescents and caregivers. Although the data from the feedback reports will come from adolescent and caregiver participants, the data will be distributed in aggregate form and will be void of individual identifiers.

4.4 Data storage and confidentiality

One month prior the adolescent's scheduled appointment with their PCP, participating PSPRN clinics will generate reports with potential participants' contact information from electronic scheduling tools which will be provided to study staff. We will request a full waiver of authorization under HIPAA to obtain contact information for individuals who have scheduled an appointment at the participating clinics. We will collect the minimum amount of information necessary to identify potentially eligible participants from the participating clinics' electronic scheduling tools. Data used include: caregiver/guardian name, adolescent name, age, date of appointment with PCP, address, and telephone number. Contact and identifying information will be used solely for study recruitment purposes and will only be accessible to study staff with a direct need to access this information (e.g., research staff mailing letters and conducting phone screening). We will assign a unique study number to individuals for recruitment purposes. This study number is then used in study files, rather than subjects' names. We will then maintain and protect a linking file which links study number to participants' names and other identifying information including participants' e-mail addresses and cell phone numbers. This linking file will be stored in Seattle Children's Research Institute (SCRI) on a secure database on the SCRI network. Access to the SCRI network is controlled by valid, networked user accounts which include study researchers and staff. Identifying information used to recruit participants will be destroyed within 5 years of the end of the study. SCRI is responsible for storage of data collected from participants. Study data for enrolled participants will be identified by study IDs and will also be retained in a SCRI secure database on the SCRI network. Analytic data files will contain no identifying information.

Subject demographic data will be recorded in a password-protected database. Completed questionnaire data will be collected through DatStat Illume, a platform used to develop secure, web-based surveys, and then exported from DatStat Illume into SPSS, Stata/SE, and SAS for analysis purposes. Data are stored on a secure SQL server, and are available to study investigators for queries, reports, and download for analysis.

Web-based surveys will be accessed by logging on to a secure server with security and data integrity violations obviated by requiring participants to log in with a password unrelated to any identifying information on any on-line page or database. All information transferred between client and server machines will be secured using 128-bit encrypted Secure Sockets Layer. All data stored in the online repository will be encrypted using the official Advanced Encryption Standard algorithm. Protocols have been informed by prior internet-based studies conducted by study investigators.

For participants enrolled in the post-implementation period, their baseline report will be printed by study or participating clinic staff and given to the participant's PCP prior to their appointment. Participant reports will be shared with PSPRN staff via a protected, designated fax machine available only to clinic staff and providers or through a secure server with security and data integrity violations obviated by requiring them to log in with a password unrelated to any identifying information related to the research participant. All information transferred between client and server machines will be secured using 128-bit encrypted Secure Sockets Layer. All data stored in the online repository will be encrypted using the official Advanced Encryption

Standard algorithm. Protocols have been informed by prior internet-based studies conducted by study investigators.

For purposes of analysis and manuscript preparation, paper data files will be maintained for up to 3 years after the project ends, after which all paper data will be disposed of via shredding. Secure electronic data files will be kept for up to 7 years after the project ends on SCRI's secure network.

5. Risk/Benefit Assessment

5.1. Risk Category

This is a minimal risk study, with the probability and magnitude of discomfort no greater than ordinarily encountered in daily life or during the performance of routine psychological examinations/tests or medical care. We will request a Full Waiver of Authorization under HIPAA for waiver of documentation of consent and waiver of the requirement for signature on the authorization for use and disclosure of health information.

5.2. Potential Risks and Protection Against Them

5.2.1 Risks.

We foresee two potential risks to study participation. The first risk is that we may discover a harmful behavior requiring urgent intervention such as suicidality. Youth with concerns for suicidal ideation on the PHQ-9 (reporting "thoughts of being better off dead or of hurting yourself in some way" several days or more) will be asked two additional questions from the Teen Screen (www.teenscreen.org) version of this questionnaire asking if: a) in the past month the youth has had "serious thoughts about ending your life" and b) they have ever made a suicide attempt. Further details on addressing suicidality are provided below. The second risk to participants is that the information provided on the Check Yourself app may not remain confidential. The PCP may choose to put risk behavior information in the youth's electronic medical record. It is also possible that youth may leave their computer screen with information from the Check Yourself app open in their web-browser and someone else might see it. Although we will emphasize the importance of completing the survey in a private setting, participants may still complete the Check Yourself app in an open setting (i.e., computer in the family room) and other family members might observe their responses.

5.2.2 Protections against Risks.

All research activities will be reviewed and approved by Seattle Children's IRB as well as clinic-specific IRBs (when required) to ensure participants are adequately protected against risk and all research activities are HIPAA compliant. Participants will be fully informed of the potential risks of participation, alternate treatment options, and their right to discontinue study participation at any time. Specific steps we will take to reduce known risks are described below:

5.2.2.1 Confidentiality and Protections.

As part of the consent procedures, adolescents and caregivers will be informed that the adolescent should complete the assessment privately and adolescents will be instructed to exit the web browser at the completion of the survey. Data collected from the web-based screening survey at baseline may be shared with treating PCPs. Data collected during all follow-up assessments, including receipt of counseling on each of the targeted behaviors, visit satisfaction, and receipt of follow-up will be given to providers in aggregate form, segregated by clinic and will be void of individual identifiers. All other data will be held confidential and will not be shared. At each contact, study materials will clarify the nature of data collected and whether data will be shared with treating PCPs. Study materials will also outline situations in which results may need to be shared with caregivers (i.e. suicidal thoughts). All materials included in the chart by PCPs will be considered part of confidential patient data and will be bound by customary restrictions on access to patient records. For example, Washington State law requires consent of the youth to release information regarding their mental health, sexual health, and alcohol and drug use. It should be noted that screening of health risks including depression, sexual activity, and alcohol use is a routine and recommended aspect of adolescent clinical care. All study data will be securely stored in either password-protected computer files or in locked file cabinets and identified with study IDs (see section 4.4 for specific data security measures).

5.2.2.2 Management of suicidality.

Regardless of intervention status, participants with a positive response on the items assessing suicidality will be flagged for further evaluation during their appointment with the PCP. Additionally, research staff will track all flagged youth to ensure that an assessment is completed by one of the study clinicians. A study clinician (Dr. Richardson, a board certified Adolescent Medicine Provider, Dr. Spielvogle, a licensed mental health counselor, or Dr. McCarty, a licensed clinical psychologist) will call to evaluate any youth with a positive response on items assessing suicidality using a protocol that we have employed in our prior depression studies and will assist in connecting the youth with care based on the level of assessed risk. The assessment consists of a semi-structured interview, including questions about pervasiveness of thoughts, impulsivity, presence of a plan and current supports, with guidance for assessing risk. All youth judged to be at higher than minimal risk will be encouraged to seek care and assisted with identifying an appropriate resource (PCP, mental health specialty care, emergency services) based on severity. Youth who are found to be actively suicidal will be assisted with receiving resources within 24 hours. Youth who are at low risk will be assisted with connecting with the PCP within 1-2 weeks. For youth <18 years old who are found to be at higher than minimal risk, the investigator will also speak with a parent/guardian to share recommendations and offer assistance in accessing care. Consent procedures will make clear the situations in which a caregiver would be notified using standard clinical language regarding danger to self or others. This protocol has functioned smoothly in each of our prior studies, and youth and caregivers have expressed gratitude for the information provided and for additional assistance in receiving care.

5.3. Potential Benefits

5.3.1 Individual Benefit (other than remuneration).

All participants may receive some satisfaction or indirect benefit from contributing to this research. PCPs may benefit from the training they will receive on adolescent-centered preventive counseling, which may increase their motivation, self-efficacy, and skills to address challenging behaviors and provide MOC 4 and CME credits. Adolescents may benefit from the additional training provided to their PCPs in addressing preventive and high-risk health behaviors. Post-implementation youth participants will receive personalized feedback aimed at increasing their readiness for the visit and motivation for healthy behaviors, which may have a positive impact on their health.

5.3.2 Societal Benefit.

Potentially preventable health-compromising behaviors are among the leading causes of morbidity and mortality in the adolescent age group. Screening and preventive interventions are recommended by multiple professional organizations, but are often not performed. This project takes an innovative strategy of training PCPs to deliver preventive counseling in adolescent-centered ways, testing this approach in tandem with a tool that provides personalized feedback for adolescents and decision support for PCPs.

This project will be an important contribution towards developing intervention strategies that are adolescent-centered and can be broadly disseminated to reduce health compromising behaviors in primary care settings. Society and healthcare settings will benefit from the knowledge gleaned regarding these innovative tools to enhance adolescent preventive counseling quality and delivery. In this regard, the minor risks incurred are outweighed by the anticipated benefits.

5.4. Alternatives to Participation

Participation is voluntary and discontinuation is an option at any time during the study.

6. Recruitment and Consent

6.1. Recruitment Method

We plan to recruit approximately 5 providers from each of the participating clinics using the following methods (a total of 30 providers). First, we will develop a study overview sheet outlining the I-ACT intervention and study protocols and expectations. We will present information on the study with this study sheet at a provider meeting in each clinic. We will ask providers to indicate their interest in the study and will set up appointments to review and obtain consent.

Staff from Seattle Children's Research Institute (SCRI) will recruit and enroll adolescent and caregiver participants through a rolling recruitment process, organized by clinic.

Potential participants will be identified up to six weeks before their scheduled appointment via a data pull from the clinic scheduling software. Research staff will mail an Introductory Packet to the youth's home containing:

- Introductory letter signed by the clinic with an opt-out phone number
- Introductory flyer
- Study Information sheet

We will request a full waiver of authorization under HIPAA to obtain contact information for potential participants. Our procedure will be:

1. Contact the caregiver by phone
2. Screen for eligibility, explain the study, and answer questions. If the caregiver wishes to participate, study staff will arrange a meeting with the caregiver and adolescent via telephone to review the study information sheet and obtain oral consent/assent.

"Adult adolescent" (i.e. 18 year old) recruitment: "Adult adolescents" will be approached before their caregiver. Study staff will attempt to contact the "adult adolescent" by phone. Once the "adult adolescent" is contacted, study staff will explain the study, give detailed information, and answer questions. If the "adult adolescent" wishes to participate, staff will arrange a meeting with the adult adolescent via telephone to obtain oral consent. Then the caregiver will be approached and asked to participate in the parent survey portion of the study if the teen consents to us contacting and inviting the parent. "Adult adolescents" will not be excluded from the study if their parents do not participate.

6.2. Consent and Assent

We are requesting a waiver of documentation of consent/assent and waiver of Authorization under HIPAA. This research study poses no more than minimal risk to research participants and the screening questions are standard of care. We are requesting this waiver because, whenever possible, we intend to deliver the online screening survey and follow-up visits via the internet, rather than in-person. Thus it would not be practicable to obtain written parental consent and assent if study visits are completed online.

6.2.1 PCP oral consent will be obtained

Oral consent will be obtained prior to study initiation. The study information sheet will include the required elements of authorization under HIPAA.

6.2.1 Parent oral consent and permission and oral assent.

Oral parent consent and permission will be obtained over the telephone, prior to the youth's appointment at a mutually agreed upon time. The study information sheet will include the required elements of authorization under HIPAA.

6.2.2 *Minor adolescent oral assent*.

Study staff will reach the minor adolescent by phone to explain the study. Assent will be obtained in conjunction with the oral parental consent and permission.

6.3.1"Adult adolescent" oral consent will be obtained via telephone.
"Adult adolescents" may participate in the study even if their parent does not participate.

6.3. Subject Capability
All potential subjects will have the capacity to give consent.

6.4. Subject Comprehension
Interested *caregivers* and *PCPs* will have the opportunity to discuss the study with SCRI staff prior to enrollment. Throughout this conversation, SCRI staff will assess parental and PCP understanding of the project and of participation expectations by asking parents and PCPs to use their own words to describe the project and their role in it. Efforts to clarify and simplify the research and parent's/PCP's role will be prioritized. Additionally, staff will provide reminders that parents and PCPs retain the right to withdraw from the study at any time. SCRI staff will invite questions from the parents and PCPs, reiterate their right to refuse participation, and ask whether they are comfortable with participation.

Interested *adolescents* will also have the opportunity to discuss the study with SCRI staff prior to enrollment. Throughout this second conversation, SCRI staff will assess teens' understanding of the project and of participation expectations by asking them to describe the project in their own words. Staff will remind youth that they can withdraw from the study at any time without adverse consequences. SCRI staff will encourage questions, reiterate the right to refuse participation, and ask whether they are interested in participating.

6.5. Consent Forms
Consent forms for parents and adolescents will be included with the submission to the SCRI IRB.

6.6. Documentation of Consent
Caregivers, adult adolescents, and PCPs may consent orally and adolescents may provide oral assent. Documentation of oral consent and assent will be noted by research staff and kept in study files.

6.7. Costs to Subjects
There are no study-related costs for any participants.

6.8. Payment for participation
Adolescents will be given $20 for completion of the baseline screener and $20 for each follow-up assessment (up to $100). Caregivers will be given $10 for each completed brief caregiver survey ($10 baseline + $10 1-day follow up =$20 total).

6.9. HIPAA

The SCRI IRB requires that research participants provide authorization to use their protected health information in connection with research. We have identified the information that will be collected from participating clinics. We will provide participant protected health information to PCPs including specific information on the adolescent's responses, which will allow PCPs to reinforce healthy behavior choices and implement further brief in-person interventions for moderate to high risk adolescents. Although a participant's responses to the health screening survey constitute protected health information generated from the research study, since the results are shared with the participant's PCP for treatment and/or health monitoring purposes, this disclosure appears to fall within an exception of the minimally necessary requirement of the Privacy Rule (Section 164.502). Thus, we will request a waiver of documentation of consent and waiver of the requirement of signature on the Authorization. As detailed above in the data storage section, all information will be collected through fully secure sites and all participants are coded to prevent identification of individuals.