Title of Study: An Intervention to Reduce Second Hand Smoke Exposure among Pediatric Emergency Patients

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ABSTRACT

Caregiver smoking is an important cause of morbidity and mortality in both adult smokers and their children who are involuntarily exposed to secondhand smoke (SHSe). Our research has found that caregivers who visit the Pediatric Emergency Department (PED) with their children have a high prevalence of smoking (up to 48%), their children have high levels of SHSe equivalent to that of active smokers, and they regularly use the PED for nonurgent, SHSe-related complaints. These smokers are motivated to quit and eager to receive cessation counseling in this setting. Annually, more than 3 million PED visits involve treatment of children with SHSe-related illnesses. These visits provide a unique "teachable moment" to motivate caregiver quitting, given the relationship between quitting and improvements in their child's health. Because of the long, unavoidable wait times and the frequent use of the PED for non-urgent care, this is an ideal venue for intervening with this population. Moreover, we and others have demonstrated the feasibility of conducting complex randomized trials in PEDs without disrupting clinical flow. Building on our prior research, we propose to conduct the first randomized trial to test whether a cessation intervention in the PED setting can reduce caregiver smoking and decrease children's SHSe. This study will test the efficacy of a cessation intervention for caregivers in a large, inner-city PED that is a major nodal site for the federally funded Pediatric Emergency Care Applied Research Network (PECARN). The proposed Screening, Brief Intervention, and Assisted Referral to Treatment (SBIRT) will highlight the effects of SHSe on their child's health. We will randomize 750 caregivers who smoke who present to our PED with their child who has a SHSe-related illness to either one of two conditions: 1) SBIRT; or 2) Healthy Habits Control (HHC). The SBIRT condition will use components shown to be effective in the out-patient setting but not yet tested in the PED setting. It will include a brief form of the Clinical Practice Guideline: Treating Tobacco Use and Dependence, motivational interviewing, engaging and personalized materials on the effects of smoking and SHSe, immediate access to caregivers' choice of cessation resources (e.g., Quitline, smokefree.gov, or smokefreeTXT), a 12-week supply of nicotine replacement therapy and booster materials for 12 weeks. The HHC program has been previously developed and used in the out-patient setting, and will be used as an attention control in which caregivers will receive instruction on healthy lifestyle choices to improve their child's health. Cessation assistance will be offered at the study's conclusion. If effective, the SBIRT model could be routinely used in the PED setting, which could reach at least one million smokers a year, and could result in significant reductions in caregivers' tobacco use, SHSe-related pediatric illness, and costs in this population. In addition, our results will inform the conduct of public health research efforts aimed at adults via the PED. If successful, we will create a comprehensive package of materials for disseminating the implementation of the intervention throughout PECARN and non-PECARN PEDs, and EDs nationwide. This study will also assess the prevalence and correlates of cannabis smoke exposure (CSE) among PED patients who are in the SHS-exposed group.

PURPOSE

We propose to conduct the first randomized controlled trial to test whether a cessation intervention in the PED setting can reduce caregiver smoking and decrease children's SHSe.

Primary Aim 1: To evaluate the efficacy of the SBIRT compared to Healthy Habits Control (HHC) condition. Primary outcomes are self-reported prolonged abstinence and point prevalence at 6-weeks and 6-months post-enrollment, validated in all participants via expired carbon monoxide and salivary cotinine. Secondary outcomes include number of cigarettes smoked, quit attempts, readiness to quit, and use of cessation resources.

Hypothesis 1: Caregivers who receive the SBIRT will have higher prolonged abstinence and point prevalence cessation rates compared to caregivers in the HHC condition.
Primary Aim 2: To evaluate the efficacy of the SBIRT on reducing children's SHSe. Outcomes are caregiver reports of total home/car smoking bans and reductions in SHSe (validated using salivary cotinine in children).
Hypothesis 2: Children of SBIRT caregivers will have higher total home/car smoking bans and lower home/car smoking exposure compared to children of HHC caregivers.
Primary Aim 3: To explore mediators and moderators of the SBIRT outcomes.
Hypothesis 3: The SBIRT intervention effect on prolonged abstinence and point prevalence cessation rates will be mediated by the caregiver's perception of the risk of smoking on their child's health and the caregiver's motivation to quit over time. The intervention effect will be moderated and attenuated by factors such as household smokers, financial strain, and low social support to quit.
Secondary Aim 1: To conduct a cost analysis to determine the numbers of SHSe-related PED visits and hospitalizations in children of caregivers in the SBIRT condition compared to children of caregivers in the HHC condition. This will provide a basis for a future, full-scale cost-benefit analysis.
Secondary Aim 2: Using the findings from this project and our prior research, we will develop a manual of operations and a comprehensive package of provider and patient materials that will be disseminated for use in other PEDs and EDs nationwide.
Secondary Aim 3: To quantify the prevalence and identify correlates of Cannabis Smoke Exposure and SHSe among SHS-exposed PED patients.

Exploratory Aim: To examine the DNA methylation (DNAm) patterns and associated clinical patterns in female children of smokers and their mothers compared to a control group of female children of nonsmokers. We will use cheek (buccal) swabs that have been collected from participants in this Aim. We will measure genome-wide gene expression and DNAm patterns to identify and compare differentially methylated cytosine-[phosphate]-guanine (CpG) loci in children of smokers and their mothers, and children of nonsmokers, focusing on loci implicated by previous studies. We will also examine the association between DNAm levels compared to cotinine levels and maternal-reported TSE patterns in children, maternal-reported tobacco use patterns, and child illness types.

BACKGROUND

Involuntary exposure to secondhand smoke (SHSe) from caregivers who smoke is an important cause of morbidity and mortality in children. Annual healthcare costs associated with SHSe and adult smoking are over $100 billion and increasing.[1] Our research has found that among children who visit the Pediatric Emergency Department (PED), there is high prevalence of caregivers who smoke (up to 48%) and children of these caregivers have high levels of SHSe equivalent to that of active smokers. These smokers have incomes at or below the poverty level (over 50%), have limited access to cessation resources, and frequently use the PED as a "safety net" for non-urgent, SHSe-related complaints such as colds and ear infections.[2-6] In 2010, 56% of the 29.8 million emergency department visits for children were triaged in the non- or semi-urgent category and these rates were highest in those who were uninsured or Medicaid recipients.[7,8] These families are at increased risk for a variety of tobacco-related disparities including differences in: tobacco use, cessation rates, access to cessation resources, and adult and pediatric tobacco/SHSe-related morbidity.[9-13] Encouragingly, these caregivers are motivated to quit and eager to receive cessation interventions in this setting.[4,14-16]

Annually, more than 3 million PED visits involve treatment of children with SHSe-related illnesses.[8] These visits provide a unique "teachable moment" in which providers can leverage the caregiver's desire to quit and the child's current SHSe-related health condition.[17-19] Moreover, the PED is an ideal venue for intervention as the environment already entails long natural wait times for non-urgent care, during which we and others have shown that even complex randomized trials can be achieved without disrupting clinical flow.[20-22] *The proposed study will be conducted in a PED that is one of the 7 main nodes in the federally funded Pediatric Emergency Care Applied Research Network (PECARN) which consists of 18 PEDs that conduct active clinical research with over 1 million children.*[20-25] ENREF 16 Although cessation research has been conducted in the adult ED,[25-27] large controlled trials of interventions for adult caregivers in the PED have not been conducted. We propose a study that will represent an evolution in the use of the PED to improve the health of both caregivers and their children. The results of this trial would move the field forward, as the provision of cessation interventions for the caregiver, *who is not the patient*, is quite different than for an *adult patient*. Furthermore, the need for such interventions in

the PED setting is especially timely given the federal mandate for healthcare organizations to better manage population health in ways that will enlist providers to deliver more comprehensive and efficient care[28-30] The proposed project is responsive to the mandate to help the "population to feel empowered to manage its health" thus "reducing the supply (and the demand) of unnecessary care".[29]

Low-cost interventions that will reduce tobacco-related consequences in caregivers, especially in low income caregivers with young, racial/ethnically diverse children, are urgently needed in the PED setting.[26,31-33] The potential impact of such interventions, defined as reach (the number of people who would use the intervention) multiplied by efficacy (percentage of people who use the intervention), could have a substantial public health impact.[34] For example, of the 3 million PED visits for SHSe-related illnesses, we can conservatively estimate that 35% are by caregivers who smoke and their children. Of these 1.1 million visits, if 20% of these caregivers quit, this equals over 200,000 new ex-smokers as a results of PED cessation interventions, annually.[26,35] This will translate into many more children who will no longer be exposed to SHS in their homes, which will result in lasting pediatric health benefits and decreased child healthcare costs.

Furthermore, the proposed project also represents an evolution in the use of the PED visit to conduct theoretically grounded research in this unique setting that can be used to target and improve the health of both adult smokers and children. The results will improve our understanding of how to conduct and interpret the results of health behavior research in this setting. The knowledge gained will have applications in other adult evidence-based public health behavioral interventions in this setting. The results may be translated into other interventions in which screening and counseling is given to adults who bring their children to the PED such as interventions related to alcohol and drug use, domestic violence, and HIV testing and treatment.[36,37]

Another aim of the project is to explore prevalence and correlates of cannabis smoke exposure (CSE) among PED patients who are in the SHS-exposed group. Trends reveal cannabis smoking is almost four times more common among cigarette smokers who live with children than among nonsmokers.[38] Thus, cannabis smoke can also be involuntarily inhaled by children, and may be harmful to their health.[39] Other smoke exposure-related chemicals (e.g., volatile organic compounds[40]) are also harmful to child health.

The prevalence, risk factors, and clinical effects of child cannabis smoke exposure (CSE) compared to SHSe is also important to understand. However, little is also known on the prevalence of CSE and SHSe among PED patients and related risk factors, health effects, and healthcare utilization. There is currently no precise estimate of CSE among SHS-exposed children. Therefore, this study will also quantify the prevalence and identify correlates of CSE and SHSe among SHS-exposed PED patients.

METHODS

Study Design Overview

Design. We will use a randomized, two-group design for the proposed study. We will recruit 750 caregivers who smoke and present to the PED with their child for a SHSe-related chief complaint. Participants will be randomly assigned to one of two study conditions: (1) Screening, Brief Intervention, and Assisted Referral to Treatment (SBIRT) Condition or (2) Healthy Habits Control (HHC) Condition.

Pool of Potential Participants: Approximately 6,000 pediatric patients with a SHSe related illness will present to the PED with their caregiver in a 30 month period. Based on our research, we know that approximately 85% of caregivers (N=5,100) will be able to be screened by a Clinical Research Coordinator (CRC); at least 35% will be smokers (N=1,785); and at least 80% of these caregivers will consent (N=1,428).

Assessments. Caregivers will complete an informed consent. They will also complete the baseline electronic assessment on a study tablet. Caregivers will be assessed with questionnaires at baseline, approximately 6-weeks, and approximately 6-months post-enrollment. We will also contact participants via text messaging, email, phone, or social media to remind them of study participation. Should we discover any missing data, we may call participants or conduct home visits at any time point during the study. Before conducting these additional home visits, we would contact the participant first to obtain permission to conduct the home visit. We will assess all children at baseline and at approximately 6-weeks post-enrollment. At 6-weeks we will contact participants via phone calls, emails, social media, text messaging,,and home visits to children and caregivers in the SBIRT and HHC condition to: 1) verify abstinence on 100% of caregivers who report that they have not smoked in the past

7 days via expired carbon monoxide testing and/or salivary cotinine, 2) obtain a follow-up salivary cotinine level on 100% of children to validate total smoking bans, and 3) complete assessment of outcomes. At 6 months, we will assess all caregivers via phone or email. We may contact them via social media or text messaging as well. Participant's privacy will be maintained when contacting them through social media by sending messages that only the participant can see via social media. PHI will not be used on these messages. Should the caregiver report abstinence and smoking bans, a home visit will be conducted to validate self-reported abstinence and total home smoking bans via salivary cotinine on the child and via expired carbon monoxide testing and/or salivary cotinine on the caregivers during home visits. Follow-ups may be conducted at CCHMC hospital if the participant already has a scheduled appointment at the hospital. If study staff is unable to make contact with the family during the course of the study to schedule the follow-ups an unannounced home visit may be conducted in order to complete study procedures.

Randomization. We will stratify by gender of the primary caregiver and stage of readiness to quit smoking where participants will be in stages 1: pre-contemplation, 2: contemplation 1 or 2, or 3: preparation;[41,42] thus there will be 8 strata for randomization. A random block randomization scheme will be compiled by the study biostatistician prior to the start of the study, and used by the CRC to allocate participants to each condition. The biostatistician has a SAS® program for creating the randomization scheme that has been tested and used for other studies. As it is anticipated that there will be fewer male caregivers, the random blocks used will be smaller than for the females. The randomization scheme will be accessed by the CRC by logging into a dedicated website and entering the gender and readiness to quit stage, the study group assignment and a study identification number will be returned. Backup will be opaque envelopes, kept within the PED with stratification and study identification number marked on the outside.

Delivery of the SBIRT and HHC. Six or more clinical counselors/intake coordinators/research coordinators will be available in the PED to deliver the SBIRT and HHC[43] _ENREF_65 interventions. The use of clinical counselors/intake coordinators/research coordinators will increase the generalizability of the intervention, as most U.S. emergency departments have clinical counselors/intake coordinators/research coordinators available.

Resources for quitting marijuana use: Should participants report that they are current marijuana users, they will be offered information to help them quit marijuana use.

Setting. This study will occur in the main PED or in the Urgent Care of CCHMC.

Clinical Counselor/Intake Coordinator/Research Coordinator Activities, Training, and Monitoring

Three or more clinical counselors/intake coordinators/research coordinators will deliver the SBIRT intervention and three or more clinical counselors/intake coordinators/research coordinators will deliver the HHC intervention to caregivers while their child is waiting to be seen in the PED. All clinical counselors/intake coordinators/research coordinators will receive formal motivational interviewing (MI) training from an MI expert. This training, followed by booster session(s) after approximately 6 months or more, will teach them how MI can be used as a collaborative, person-centered form of guiding to elicit and strengthen motivation for change and will help them use specific skills related to MI. Clinical counselors/intake coordinators/research coordinators will be trained in MI strategies and techniques. The MI trainer will review a selection of audio recordings of each clinical counselor/intake coordinator/research coordinator chosen randomly throughout the study period and they will receive individualized feedback on these sessions from the MI trainer. The reviews will be spread out over the course of recruitment period. The clinical counselors/intake coordinators/research coordinators' audio-recorded sessions will be independently rated for adherence using the Motivational Interviewing Treatment Integrity (MITI) system by our MI expert, who will provide individualized written and verbal feedback to each clinical counselor/intake coordinator/research coordinator.[44]These audio-recorded sessions will be collected in an ongoing basis to facilitate fidelity to MI. MI approaches have been successfully applied in the ED setting for a variety of issues, including alcohol and smoking.[45]

The clinical counselor/intake coordinator/research coordinator who delivers the SBIRT will be trained as a Tobacco Treatment Specialist at a TTS training center. This training will teach the clinical counselors/intake coordinators/research coordinators how to deliver an evidence-based, cognitive behavioral treatment for nicotine dependence. Presentations and hands-on exercises will emphasize the understanding the addictive nature of tobacco use, its impact on health, and key clinical activities for assessing and treating the nicotine dependent individual. The PI will then provide this clinical counselor/intake coordinator/research coordinator with an "Assisted Referral" training session focused on study logistics, the delivery of brief cessation and SHSe reduction

counseling, and direct connection to the QL, or smokefreeTXT, or smokefree.gov during the PED visit. The clinical counselors/intake coordinators/research coordinators will be taught to frame the messages to increase caregiver's risk perception of smoking to their child and themselves, and they will be trained to tailor the messages to motivation to quit and level of tobacco dependence. [46,47] The clinical counselors/intake coordinators/research coordinators who deliver the HHC intervention will receive training from the PI or study staff on the purpose and importance of talking to caregivers about healthy habits to improve their child's health[43] _ENREF_65 and will be given guidance on engaging and delivering the intervention to caregivers during the PED visit; barrier identification and reduction techniques will be taught.

In order to promote fidelity and uniform implementation of the SBIRT and HHC interventions, the clinical counselors/intake coordinators/research coordinators will complete a fidelity checklist after each session. Separate checklists for each condition will include key prescriptive and proscriptive elements for each condition. Sample prescriptive elements for the SBIRT include recommending total home/car bans, asking visitors to smoke outside, using NRT and other cessation resources to quit; sample proscriptive elements are the presentation of the effects of SHSe on children, brief statistics on SHSe and child health outcomes, and benefits of quitting on children. Sample prescriptive elements for the HHS include recommending 5 fruits and vegetables each day, gradually decreasing screen time, and getting kids active with fun options; sample proscriptive elements are the presentation of the health effects of poor diet and inactivity. Although completing these checklists does not ensure ideal implementation, they provide reminders to the clinical counselors/intake coordinators/research coordinators to be aware of essential features that must be included in each session. In addition, every SBIRT and HHS intervention will be audio-recorded, except in cases where the caregiver declines to be audio recorded Approximately 10% of the audio recordings will be randomly selected and independently rated by blinded reviewers for adherence to the checklists and consistent implementation of the two conditions.

Booster training sessions and problem solving sessions will occur by the PI or study staff, if needed, every several months to problem solve issues that have come up and to provide refreshers and reminders about the key elements of the intervention to prevent drift and maximize consistency.

SBIRT Condition

SBIRT Protocol. After potential participants have been identified, CRCs will obtain informed consent and enroll eligible caregivers, and collect baseline data. The clinical counselors/intake coordinators/research coordinators will then provide caregivers with the brief "Advise, Assess, Assist" intervention based on the Clinical Practice Guidelines, and tailored on levels of motivation to quit and tobacco dependence.[32] _ENREF_21 If both caregivers are present, eligible, and wish to receive the intervention, then the clinical counselors/intake coordinators/research coordinators will provide each caregiver with the "advise" portion of the intervention. However, only the primary caregiver (designated by the couple) will be enrolled in the study and assessed for data collection. The intervention components that will be provided are as follows:

1. Advise. Discuss the effects of SHSe on their child's health and the benefits of quitting, and how quitting could improve their child's medical symptoms and decrease future PED visits. Motivational interviewing (MI) techniques will be used to increase caregiver's risk perceptions of their child's vulnerability to SHSe and the health risks associated with smoking to the smoker and child. [46,49,50] The clinical counselors/intake coordinators/research coordinators will elicit the caregiver's beliefs about their tobacco use, the importance they place on quitting, and the confidence they have to quit. The clinical counselors/intake coordinators/research coordinators will ask about specific barriers or facilitators to quitting (e.g., financial stress, other household smokers, social support, home environment, prior quit attempts, and rewards associated with quitting). They will collaborate to increase confidence in quitting, problem-solve how to bypass barriers, and create action steps to quit. All caregivers will be encouraged to implement total smoking bans as a way to decrease SHSe. [51,52] For those not wanting to quit, options will be discussed, and goals set for reducing SHSe (e.g., gradually increasing the proportion of cigarettes smoked outdoors until eliminating indoor/car smoking completely).

2. Assess. The clinical counselors/intake coordinators/research coordinators will assess caregivers' readiness to quit by asking if they want to quit in the next 30 days. MI techniques will be used to increase readiness to quit for caregivers who do not express an immediate interest in quitting, as well as to solidify and maintain

commitment in those ready to proceed.

3. Assist. This step will consist of 3 components:

1) NRT: All caregivers who do not have any contraindications to NRT will be offered a free, 6 week supply of their choice of NRT patches or lozenges. . NRT will be stored in a locked cabinet in the CRC office in the PED. The clinical counselors/intake coordinators/research coordinator will screen all participants for eligibility and for any contraindications to NRT using a screening checklist (See Appendix F). If there are any questions about eligibility for NRT, the clinical counselors/intake coordinators/research coordinators will contact the PI or other study MD,. The PI or other study MD will be available in-person or by phone to address any questions. This arrangement has worked well for our most recent cessation trial (5K22CA163747). The screening checklist will be sent electronically to the PI or other study MD if there are any contraindications to NRT, who will approve/disapprove the distribution of NRT to the caregiver. If there are no contraindications to NRT on the checklist, the form will not be sent to the PI or other study MD, and the research coordinator may dispense NRT to the caregiver. Study staff will instruct the caregiver on NRT use and they may use expired NRT to demonstrate to caregivers how to place the patch on and to show them what the lozenge looks like. In addition, all caregivers will be provided a home visit for follow-up at 6-weeks during which they will be asked if they were given NRT at baseline, and if so, if they used the NRT. If they used approximately 80% of the NRT and wish to receive more NRT, they will be screened for eligibility and for any contraindications to NRT using the screening checklist in the same manner listed above as at baseline (See Appendix I). If eligible, they will receive 6 weeks of NRT. If a home visit is not possible, the survey will be completed via phone or email and the sample may be obtained from the family via mail. An approximately four week window for follow-up will be used. The follow-up may also be completed at CCHMC or another mutually agreed upon location, if the participant has an already scheduled appointment.

2) Immediate connection to cessation resources: All caregivers will be provided an "Assisted Referral" based on preference. These options will include: a) Quit Line: The clinical counselors/intake coordinators/research coordinators will dial a direct number to the Ohio QL. A QL counselor will initiate brief counseling which may include counseling calls and free NRT[53] If the caregiver prefers, a fax referral may be completed and faxed to the QL.

b) Web-based: the clinical counselors/intake coordinators/research coordinators will help the caregiver log onto smokefree.gov using the computer that is in every patient's PED room. This site has a variety of interactive tools including a LiveHelp online "chat" service, SHSe and cessation quizzes, a cessation mobile app, and other helpful resources; c) Text Messaging: the clinical counselors/intake coordinators/research coordinators will help the caregiver sign up with smokefreeTXT. These free mobile services provide encouragement, advice, and tips to help smokers quit.

3) Intervention Materials: To supplement the baseline intervention, we will provide free caregiver materials shown to be effective in previous studies[54,55] (See appendix B). All or some of the materials listed in Appendix B will be provided to the caregiver, as applicable. Booster messages with reminders of the benefits of quitting will be sent by email, mail, or text message for 12 weeks.

Feasibility and Generalizability: The SBIRT is feasible for deployment in PEDs and general EDs that serve both children and adults. The vast majority of these settings have clinical counselors/intake coordinators/research coordinators or equivalent professionals who could be trained to deliver the intervention. SBIRT is streamlined and efficient and can be integrated into acute care. Even in the most time-efficient ED settings, waiting times are inevitable. These provide opportunities for delivery of the SBIRT. The format of the intervention mirrors other successful prevention approaches in the ED setting. Our association with PECARN provides an infrastructure for rapid deployment of the intervention dissemination materials leading to widespread adoption.

The Healthy Habits Control Condition

Rationale for the use of an attention control condition. We will use an attention control condition in order to determine the efficacy of the SBIRT condition. In a RCT examining the effects of a behavioral intervention, the use of an attention control condition helps to reduce differential attention and expectancies of treatment in the intervention, and will decrease threats to internal validity.[56-57] Controlling for attention will entail exposing control group participants to a meaningful clinical experience that takes as much time and provides as much contact with the CRC as the SBIRT. The use of this attention control condition is highly consistent with good clinical care, unrelated to the focus of the active intervention (i.e., smoking cessation), and likely to be perceived by families as both credible and useful. We will use a childhood obesity prevention program entitled "Let's Go! 5-2-1-0"

which is a program which has been developed and used in the outpatient clinic and school setting. This program is designed to help children and families eat healthy and be active, by recommending the following daily behaviors: 5 fruits/vegetables, no more than 2 hours of TV/computers, 1 hour of physical activity, and 0 sugary drinks.[43,58-60] The delivery of the HHC will mirror that of the SBIRT.

HHC Protocol. After potential participants have been identified, CRCs will obtain informed consent, enroll eligible caregivers, and collect baseline data. The clinical counselors/intake coordinators/research coordinators will provide caregivers with the brief HHC intervention based on the "Let's Go! 5-2-1-0" program[43,58-60] and tailored on current diet and activity levels. If both caregivers are present, eligible, and wish to receive the intervention, then the clinical counselors/intake coordinators/research coordinators will provide each caregiver with the recommendations. However, only the primary caregiver (designated by the couple) will be enrolled in the study and assessed for data collection. The intervention components that will be provided are:

1. Advise. Caregivers will be advised by the clinical counselors/intake coordinators/research coordinators about helping their kids and families to eat healthy and be active. He/she will give them recommendations on daily nutritional and healthy lifestyle guidelines with the 5-2-1-0 behaviors. MI techniques will be used to increase caregiver's risk perceptions of the benefits of healthy choices and the clinical counselors/intake coordinators/research coordinators will ask about specific barriers or facilitators to making and adhering to these choices.

2. Assess. The clinical counselors/intake coordinators/research coordinators will assess caregivers' readiness to make good lifestyle choices by asking which area of the 5-2-1-0 recommendations they want to improve in the next 30 days. MI techniques will be used to increase readiness to change habits for caregivers who do not express an immediate interest, as well as to solidify and maintain commitment in those ready to proceed.

3. Assist. This step will consist of the following components:

1) Water bottle : All caregivers will be offered a free colorful water bottle to encourage children to drink more water.

2) Immediate connection to 5-2-1-0 resources: All caregivers will be provided with the option to view a 5-2-1-0 blog that has ideas on how to stay healthy such as ways that families have celebrated holidays without extra sugar and fats; ideas for non-TV or video game related activities; and information on how to read food labels.

3) Intervention Materials: To supplement the baseline intervention, we will provide free caregiver materials used in other healthcare setting (see appendix C). All or some of the materials listed in Appendix C will be provided to the caregiver, as applicable. These materials are downloadable from www.letsgo.org.[68,91-93] The caregivers will receive email/mail/text messages (caregiver's preference), for 12 weeks, reminding them of healthy lifestyle behaviors. At 6-weeks we will contact participants via phone calls, emails, text messaging, social media, and home visits to children and caregivers in the SBIRT and HHC condition to: 1) verify abstinence on 100% of caregivers who report that they have not smoked in the past 7 days via expired carbon monoxide testing and salivary cotinine, 2) obtain a follow-up salivary cotinine level on 100% of children to validate total smoking bans, and 3) complete assessment of outcomes. At 6 months, we will contact all caregivers via phone, text messaging, social media or email. Should the caregiver report abstinence and smoking bans, a home visit will be conducted to validate self-reported abstinence and total home smoking bans via salivary cotinine on the child and via expired carbon monoxide testing and/or salivary cotinine on the caregivers during home visits. Follow-ups may be conducted at CCHMC hospital if the participant already has a scheduled appointment at the hospital. If a home visit is not possible, the assessments will be conducted over the phone or via email. An approximately four week window for the follow-up assessments will be used.

At the study's conclusion, the HHC group will be given brief information regarding resources for quitting smoking over the telephone. A script will be used by the research coordinator to provide this information.

Screening for missed eligible patients

We will assess for missed eligible patients by screening for, but not limited to, second hand smoke exposure complaints in children 0-18 years old through our EMR periodically, and a chart review will be completed for those not enrolled in the study to gather data about missed eligible patients. We are requesting a waiver of consent to review these patients' charts. Data about missed patients may be used to assess screening hours as well assess for training needs when missed eligible patients are identified during screening time. Missed eligible data will include the patients' encounter ID and medical record number, arrival date and time, age, who escorted the patient to the ED, triage code, spoken language, chief complaint and arrival complaint, triage start

time, departure time, disposition, city, state, and zip code, and if they were screened for another study. We will also examine the charts of all children screened during the study period to determine the sociodemographics, geographic variability, and clinical characteristics of the entire screened population. We will conduct a chart review to extract data on their demographics, zip codes, address, clinical findings, medical test results, treatment, disposition, and healthcare visit patterns. Again, we are requesting a waiver of consent to review these patient's charts. These patients cannot be consented prior to participation. However, their rights and welfare will not be affected by the data collection. The patients' data will be the same as those consented into the study and they will still receive the same care regardless of study participation.

Participant Screening, Enrollment, and Exclusion

During the approximately 48-month or longer study enrollment period, CRCs and approximately 1-2 pairs of clinical counselors/intake coordinators/research coordinators (i.e., one from each condition) will provide study coverage every weekday. This increases the opportunities for recruitment and delivery of the interventions. Our prior research demonstrates that approximately 3 CRCs will be more than adequate to recruit 750 caregivers. Enrollment times will represent peak PED volumes. CRCs will screen consecutive caregivers of patients presenting to the PED using CCHMC's EMR system, Epic. CRCs will identify caregivers by reviewing Epic records of registered patients. A secure database will be used which will include all patients, their age, gender, race, chief complaint, enrollment status, and reasons for non-enrollment.

Eligible caregiver adult participants must: 1) be > or equal to age 18; 2) be accompanying a child 0-17 years of age 2) be a daily smoker; 3) speak and read English (if shown to be efficacious, we will translate the intervention materials and test it with multi-lingual CRCs and clinical counselors/intake coordinators/research coordinators in a future trial), 4) have a permanent address and a working cell or landline number, 5) live within an approximately 50 mile radius of CCHMC (since we will conduct home visits.)

Eligible child participants must: 1) Not be a current smoker of tobacco or marijuana; 2) present to the PED with : (a) a stable condition, that is, patients who are not critically ill and do not require immediate treatment and intervention by the PED practitioner (triage levels 2-5) and (b) a potentially SHSe-related complaint (which will include complaints such as wheezing, difficulty breathing, cough, ear infection, cold, ear pain, runny nose, congestion, flu, asthma, shortness of breath) as outlined by the U.S. Surgeon General;[48] or SHSe-related discharge diagnosis.

If both caregivers are present and eligible, they will be asked to identify the primary caregiver and if one or both want to receive the intervention. Although both caregivers may receive the intervention, only the primary caregiver will be enrolled and assessed for data collection. Based on our previous studies, we know that both caregivers are present in the PED and eligible for the study less than 5% of the time. Child participants will be excluded if they have a tracheostomy. Adult caregivers will be excluded if they are tobacco chewers only, using pharmacologic cessation treatment, plan to move within the study period (if they do not know their new address), or do not have a working phone number or permanent address The CRC will obtain informed consent.

For the CSE study aim, caregiver survey data on cannabis use and child CSE and stored child urine samples will be assessed from the child-parent participants in the SHS-exposed group who consented to providing this additional data and child urine samples. Eligibility criteria for the CSE study aim of this project are the same as the SHS-exposed group, and with the additional eligibility criteria that they will have: caregiver survey data on cannabis use and child CSE; a sub-sample of children have stored urine samples available for lab analysis of biomarkers of exposure; and provided informed consent to analyze the associated data and child urine samples.

POTENTIAL BENEFITS

There may be no direct benefit to adult participants other than the counseling and NRT that they will receive from the study in the intervention condition. The intervention may help them decrease their smoking. Cessation would reduce their risk of contracting lung and/or oral cancer, chronic obstructive pulmonary disease, coronary heart disease, or periodontal disease. Intervention participants will become more aware of the health risks

associated with smoking cigarettes than they may have had prior to their participation in this study. Even if they do not make a quit attempt, they will have been given information on how to go about quitting that could be useful to them in the future.

There is no direct benefit to the children of participants. However, there is a potential indirect benefit to the children of the caregivers in the intervention condition: if their caregivers quit or decrease their smoking habits, then their children will be exposed to lower levels of SHS. In addition, the benefit to society and research on PED-based cessation is potentially great. Since patients who are economically disadvantaged or of minority status use PEDs disproportionately, the results of this study may especially help determine the effectiveness of cessation interventions in this setting which could benefit society and the scientific community. The intervention may be disseminated to other PEDs if found to be effective. The risks this research may have for participation are very small but the potential benefit far outweighs the risk of slight embarrassment, increased time in the PED, potential loss of confidentiality, and risks of NRT.

POSSIBLE RISKS, DISCOMFORTS, OR INCONVENIENCES

There are 4 possible risks with respect to study participation:

(1) The potential to interfere with medical care that is ongoing: The study will specifically exclude caregivers of patients who are not medically stable during the ED visit. Only caregivers of patients who are stable, that is, who are not critically ill and do not require immediate treatment and intervention by the PED practitioner, will be eligible for enrollment in this proposed study. These patients are, by our triage criteria, clinically stable, not ill appearing, and not felt to be at high risk of deterioration or morbidity. All enrolled patients will be assessed, examined, and reassured by a triage nurse prior to enrollment. We will stress in the consent that participation in the study will be entirely voluntary and will not affect the care in the emergency department. Caregivers who participate may have an additional 30-40 minute longer ED visit time; however, the interviews and surveys will not be done while medical care is being delivered;

(2) Emotional discomfort when answering the issues raised by the interview: Some of our participants may feel uncomfortable answering some of the questions about their smoking habits, particularly in an ED setting where such questions are not anticipated. The consent form will clearly state that caregivers will be asked questions such as “Do you smoke?” and “How many cigarettes do you smoke a day?”

(3) Loss of confidentiality: Confidentiality issues dominate concerns for the successful completion of this study. Subjects are asked to provide the participants/family members/neighbor’s address, phone numbers: home number, work number, cell phone number; and email address. Participants may also be concerned about providing information on their demographics and smoking habits and the related lack of privacy. Special procedures will be put in place to assure that the data from the electronic questionnaires and follow-up questionnaires are kept secure and confidential. In addition, there is the potential for breach of confidentiality from the audio recorded sessions. In order to prevent this, no identifying information will be used in the audio recordings and the audio recordings will be destroyed at the end of the study.

(4) Nicotine withdrawal and NRT effects: If the participant quits using tobacco, he or she could experience withdrawal symptoms from nicotine cravings such as hunger, anxiety, restlessness, or sleep disturbance. Individuals who quit their addiction to tobacco products commonly experience these symptoms. If the subject uses NRT, they might experience a negative reaction. We will include a statement on the informed consent form warning of the possible side effects of NRT use, and the contraindications for use of NRT. NRT will never be dispensed without review of the caregiver’s history by the PI and CRC. In addition, detailed information on the use of Nicotine Replacement Therapy (including contraindications for use) will be given to participants. Participants will be screened by the PI (a physician) or a trained CRC supervised by the PI for eligibility for NRT use. Participants receiving NRT will be instructed to call the PI if they encounter any questions, concerns or problems related to the NRT. The PI will be available via phone or in person to provide immediate, appropriate medical advice. If any adverse reactions or complications occur as a result of this study, we will contact the Institutional Review Board (IRB) Chairperson within five working days.

Pregnancy: Pregnant smokers, nursing mothers, or women attempting to become pregnant during the course of this study will be allowed to participate in the study, but will not receive nicotine patches or lozenges.

RISK-BENEFIT ASSESSMENT

Risk-Benefit Analysis: We believe the benefits of this study outweigh the potential risks of participation. It is recommended that this proposal be classified as minimal risk with potential direct benefit to the participants.

DURATION

This project will take 7 years. In Year 1 (YI), we will: obtain IRB approval; finalize the SBIRT and HHC protocol, materials, and procedures; train CRC and clinical counselors/intake coordinators/research coordinators; provide practitioner in-services. Recruitment, follow-up assessments, and chart review to evaluate SHSe-related PED visits/hospitalizations will be complete by approximately month 54. The remainder of Y5 will be devoted to data and cost analyses; delivery of the cessation information to HHC caregivers; and if the intervention is found to be effective, the PI and Co-I (Dr. Gordon) will develop a comprehensive guide for implementation at other PEDs. In addition, we will develop dissemination and cost benefit analysis plans for CCHMC and other PEDs.

For the CSE study aim, this study has caregiver survey assessment data available from caregivers who responded to the cannabis use and child CSE questions. Stored urine samples from children in the SHSe group will be sent by CCHMC to the Centers for Disease Control and Prevention (CDC) Laboratory where they will conduct biochemical validation of smoke exposure. In Years 4-5, we will use the additional caregiver survey data on cannabis use and child CSE, electronic health record (EHR) data from CCHMC Epic, and stored child urine samples from CCHMC. In Years 5-7, we will conduct statistical analyses and disseminate the additional CSE and SHSe results via publications and presentations. It will take about 6-8 months to receive the urine sample analysis results.

DATA ANALYSIS METHODS

Data Collection, Retention Strategies, and Measures

Data Collection and Participant Retention. All baseline assessments will be electronically sent to a central, secure, HIPAA-compliant firewalled CCHMC database. We will use multiple strategies to retain the sample by relying on approaches successfully used by our PI and Co-Is in studies of high-risk, low income populations.[61-65] These strategies include: 1) Generous incentives:[15] ENREF 92 Participants will be paid with increasing compensation of $30 at baseline, $50 at 6-weeks ($20 for phone assessment and $30 for home visit), and $65 at 6-months ($30 for phone assessment and $35 for home visit); 2) Conducting home visits on all caregivers and children at the 6-week follow-up to assess outcomes and giving caregivers in the SBIRT group an additional 6 week supply of NRT if they have used approximately 80% of the NRT provided at baseline; 3) Hiring and training CRCs to carefully track participants, make home visits, and obtain follow-up data by making as many follow-up attempts as is necessary to locate participants; 4) Sending caregivers: weekly email/mail/text messages with cessation or healthy habits tips for 12 weeks, reminders of upcoming assessments. We will ask order of preference of type of reminders and follow-up; however if one technique is unsuccessful, the second and finally third choice will be used; 5) Branding study contact information in reminder postcards; 6) Collecting contact information of friends and family members completed at baseline that will contain contact information for the participant and their contacts. Cell phone numbers, e-mail addresses, and preferred times of contact will be obtained; 7) Asking our on-site Co-I (Ammerman) to provide strategies to maximize retention through thorough tracking and monitoring of study participants.8) Study staff will attempt to contact participants via phone, text, email or traditional mail in order to complete the follow-ups. In the event that a research participant becomes lost to follow-up and traditional re-contact methods (i.e. telephone, text, email, traditional mail, etc.) are unsuccessful, the use of a nationwide electronic search strategy will be employed, This will include general use of public web-based search functionality, and as a last resort, the use of a 3rd party service (Accurint). Accurint will be administered through a centralized standard process managed by the CCHMC *Center for Clinical and Translational Science and Training (CCTST)*. Only demographic information will be utilized for the purpose of facilitating the Accurint search function. Specific individual requests will be submitted to a designated member of the CCTST staff that will perform the search using the Accurint functionality. CCTST staff will provide a report back to the research team that includes the most current available contact information for the requested research participant(s). Records of each search will be maintained and available for IRB review if needed.

Given our prior experience[54] and proposed techniques, we conservatively project an 80% retention rate at 6 months.

Outcome Measures. Primary outcomes will be caregiver prolonged abstinence and 7-day point prevalence of tobacco use at 6-weeks and 6-months. Secondary caregiver outcomes will include cigarettes smoked, quit attempts, readiness to quit, and use of NRT and cessation resources (QL, smokefreeTXT, smokefree.gov). Child outcomes will be presence or absence of total home/car smoking bans, reported SHSe, and number of SHSe-related PED visits and hospitalizations at CCHMC.

Baseline Assessment. (Table 1) The brief baseline assessment (T0) will be conducted using a self-administered electronic survey to be completed on a tablet computer. The assessment items chosen are empirically validated measures from studies conducted with low-income disadvantaged study populations.[42,66-71] [39,63-68] The items are brief, easily comprehensible, and take into account low literacy levels. They are as follows:

Table 1: Measures for Baseline and Follow-up Assessments by Assessment Point	T0	T1	T2
Demographics; Financial Strain, , Household Smokers,	✓		
Tobacco Use History, Nicotine dependence, , , Motivation to Quit	✓	✓	✓
Risk Perceptions: Child; Benefits of Quitting: Child	✓	✓	✓
Child's SHSe, , Child SHSe - related PED visits or Hospitalizations	✓	✓	✓
Healthy Habits Lifestyle- daily: fruits/vegetables, screen time, exercise, sugary drinks	✓	✓	✓
SBIRT and HHC Satisfaction,	✓		
Prolonged abstinence, point prevalence, nicotine dependence, readiness to change, quit attempts		✓	✓
Cessation Resource utilization: NRT, QL, SmokefreeTXTt, Smokefree.gov, or other resources		✓	✓

1. Demographics and tobacco use. We will collect gender, age, race/ethnicity, level of education, employment status, , number of cigarettes smoked daily, time to the first cigarette of the day, nicotine dependence, number of attempts to quit >24 hours, use of pharmacological and/or behavioral treatments for quitting, motivation to quit using the Contemplation Ladder, and stage of change in readiness to quit. [41,72] Questions will also be asked about marijuana use by the participant and household members; participants will not be required to answer these questions. Participants who consented prior to Version 11 of the protocol may be re-consented at follow-up such that we may obtain information about marijuana use.

2. Financial Strain. Three items will be used to measure financial strain.[74] The questions are: "How difficult is it for you to live on your total household income right now?", "In the next three months, how often do you think that you or your family will experience a bad time such as poor housing or not having enough food?", and "In the next three months, how often do you expect that you will have to do without the basic things that your family needs?" The three items will be measured on five-point scales and averaged to create a financial strain score (α = .802). Higher scores will reflect more financial strain.

3. Risk perception to child. Perceived vulnerability regarding the effects of his/her smoking on their child will be assessed using adapted measures by Borelli et al. Perceived Vulnerability-Child will be measured with items including: "How concerned are you that smoking will make your child's illness worse?". Higher scores indicate higher perceived vulnerability.[77-79]

6. Benefits of quitting. We will assess whether the caregiver perceives that quitting smoking would have a beneficial effect on their child using the adapted precaution-effectiveness measures by Borelli, et. al. Precaution Effectiveness-Child (PE-C) will be measured by items including: "If you stop smoking, how much would that decrease your child's symptoms?". Higher scores indicate higher perceived vulnerability.[77-79]

7. Child's SHSe. Child's SHSe will be assessed by asking about family and other individuals with whom the child came in contact during the past week who smoke, locations of smoking, and number of cigarettes smoked. We will use questions adapted from previous studies.[52,80-83] Caregivers who report no smoking indoors, outdoors, or in a car will be considered to have a complete smoking ban. Epic chart review will be conducted to assess SHSe-related PED visits and hospitalizations to CCHMC for 6-months prior to baseline.

8. Healthy Lifestyle Habits. We will assess healthy lifestyle practices (daily fruit/vegetable/sugary drink consumption, daily exercise and screen time) of all children.

9. Consumer satisfaction measure. SBIRT and HHC caregivers will complete a satisfaction survey measuring intervention satisfaction and perceived usefulness.[84]

10. Secondhand and Thirdhand tobacco smoke from tobacco and marijuana exposure. There is evidence that homes of smokers of tobacco and marijuana become reservoirs of persistent toxic tobacco smoke pollutants (including nicotine, polycyclic aromatic hydrocarbons (PAH), tobacco-specific nitrosamine (TSNA), and other pollutants), to which nonsmokers may be exposed even after smoking cessation through inhalation, ingestion,

and dermal transfer. These thirdhand tobacco smoke exposure, thirdhand marijuana smoke exposure and pollution levels can be assessed by analyzing urine, and hand wipes of children and by analyzing dust and surface wipe samples from the home. Sometimes these samples can also be used to analyze secondhand smoke exposure levels as well. Thus, we may collect: 1) saliva samples from all children and hand wipe samples of all children during the baseline visit, 2) urine samples from all children who can easily urinate into a cup or bag or who urinate in a diaper if there is time during the baseline visit, 3) hand wipe samples of all children during the 6-week home/other location visit, 4) urine samples from all children who can easily urinate into a cup or bag or who urinate in a diaper if there is time during the 6-week visit, 5) home dust samples and surface wipe samples and air samples from all home visits at 6-weeks if the CRC goes to the home, 6) hand wipe samples of children that have home/other location visits at 6 months, 7) home dust samples and surface wipe samples and air samples from any home visits at 6-months if the CRC goes to the home, 8) urine samples from all children who can easily urinate into a cup or bag or who urinate in a diaper if there is time during any 6-month visits; 9) cheek swabs from the caregiver and the child at six weeks and at six months, 10) home surface area measurements. Urine collection kits may be given to participants at any of the study time points and may be mailed to, given to, or collected from participants before or after follow-up visits. Urine that is collected by participants may be either refrigerated or frozen by the participants prior to collection by study staff and delivery to the CTRC. These biological and environmental samples will be stored in the CTRC and may be analyzed for thirdhand tobacco smoke, secondhand and thirdhand marijuana smoke exposure. Once sample analyses are completed, we may examine how SHS and THS tobacco and/or marijuana levels are associated with data that may include child demographics, caregiver tobacco and/or marijuana use, home characteristics, child clinical findings, disposition, and child healthcare visits once funds become available. Participants may opt out of having their samples analyzed for marijuana smoke exposure. Participants who were consented prior to version 11 of the protocol may be re-consented at follow-up in order to use these samples for marijuana smoke exposure analyses. If the follow-up visits do not occur in the participant's home, then dust samples will not be obtained; although participants who do not have a home visit will be asked to bring a vacuum bag, if available. When funds become available, biological and environmental samples from participants and their homes will be sent to the Measurement & Evaluation Research Group (MERG) at San Diego State University Research Foundation for analysis. The San Diego State University site will be given information that may include data such as: type of specimen, study ID number, portions of baseline and follow-up assessments (including sociodemographics), and measurements and description of the area of the home sampled. Leftover samples will be returned to CCHMC. A Materials Transfer Agreement is in place which details these procedures.

For the CSE study aim, this study has caregiver survey assessment data available from caregivers who responded to the cannabis use and child CSE questions. Stored urine samples from children in the SHS-exposed group will be sent by CCHMC to the Centers for Disease Control and Prevention (CDC) Laboratory where they will conduct biochemical validation of smoke exposure. It will take about 6-8 months to receive the urine sample analysis results. Only secondary analysis of data will continue to occur at UC. A Materials Transfer Agreement will take place, which will detail the procedures for sample transfer between CCHMC and the CDC. A Data Transfer Agreement is currently in place between UC and CCHMC and details the procedures for data transfer.

We have submitted an application to The Children's Health Exposure Analysis Resource (CHEAR). As stated on the CHEAR Data Repository Data Submission Agreement: "CHEAR was established by the National Institute of Environmental Health Sciences (NIEHS) to provide analytical and laboratory services to support researchers who want to include environmental exposure assessment in their studies. If our application is

accepted, The Center for Data Science ("Data Center") at the Icahn School of Medicine at Mount Sinai will provide a data repository for storing epidemiologic and biomarker data that was previously collected in an approved CHEAR research study and for all new biomarker data generated by the CHEAR National Exposure Assessment Laboratory Network ("Lab Hubs")."

Should our application get accepted, the terms of the "CHEAR Data Repository Data Submission Agreement" and the "Data Sharing Plan for the CHEAR Data Repository" must be agreed upon and signed by the PI (Dr. Mahabee-Gittens) and an "IRB Attestation Letter for CHEAR Data Submission" from the CCHMC IRB must be signed and submitted to CHEAR.

Should our application get accepted, we will share human data and samples on those participants who consented to future research, with the CHEAR Data Repository. As per the Data Sharing Plan and the CHEAR Data Repository Data Submission Agreement, this data will include individual-level data such as "…epidemiological data, information which has been collected and recorded from study participants. These data include, but are not limited to, research and clinical assessments and information obtained via interviews, direct observations, biomarker data, records reviews, genomic data (e.g., sequence, transcriptomic, epigenomic, and/or gene expression data), psychophysiological assessments, data from physical examinations, etc. Additionally, information necessary to interpret the data (e.g., study protocols, data collection instruments, survey tools) will be shared (Please see Data Sharing Plan). The data will be submitted to the CHEAR Data Repository at the CHEAR Center for Data Science at Mount Sinai (CHEAR Data Center).

Within the embargo period, the data will be available only to the CHEAR Data Center and the Study PI through controlled-access. After the embargo period, data stripped of personal identifiers will be available through unrestricted access. All submitted data will be made available for public use access, after an embargo period, as publically accessibledatasets that have been stripped of personal identifiers. If appropriate, it is expected that the Study PI will have registered all studies in the database of Genotypes and Phenotypes (dbGaP) in addition to submitting the data to the relevant NIH-designated data repository (e.g., dbGaP, Gene Expression Omnibus (GEO), Sequence Read Archive (SRA), the Cancer Genomics Hub) after registration.

Data Submission and Release Timeline: Data that has been stripped of personal identifiers will be shared no later than the acceptance for first publication of the findings from the data set (embargo period)."

11. Clinical and cost data. We will be evaluating the clinical characteristics and associated costs/charges of the baseline visit and hospitalization (if the child is hospitalized) and any SHSe-related or other visits or hospitalizations for the period up to 12 months prior and/or 12 months after the baseline visit. We will extract clinical data and costs from the charts that may include data on the presenting illness and illness severity (e.g., heart rate, respiratory rate, oxygen saturation, physical exam findings, triage level, chief complaint, discharge diagnosis, disposition), lab tests, procedures, interventions, and test results (if any), during these visits and/or hospitalizations.

12.

Follow-up Assessments (Table 1). All participants will be assessed at 6-weeks (T1) during home visits and at 6-months (T2) via phone or email; home visits will be made to conduct biochemical validation of caregivers and children when caregivers report that they have quit at T2. We will use self-report measures of prolonged abstinence and biochemically validated point prevalence at T1 and T2 to assess cessation.[85-87] Point prevalence of tobacco use will be measured by the question: ''Have you smoked, even a puff, in the last 7 days?'' Caregivers will be considered abstainers if they report no tobacco use in the past 7 days. Prolonged abstinence will be measured by the question: ''When did you last smoke a cigarette?'' Response categories will range from ''less than 1 month ago'' to ''more than 6 months ago.'' Secondary outcomes will be assessed, including nicotine dependence, readiness to change, a quit attempt of $\geq$ 24 hours, patterns of smoking, number of cigarettes smoked/day, treatment initiation, NRT or other pharmacotherapies used, QL, text, or web follow-up. As described above, we will use measures of child SHSe to assess children's exposure and if home/car smoking bans are present. Secondary outcomes pertaining to the child's SHSe, total home/car smoking bans, and SHSe-related healthcare utilization (PED visits or hospitalizations at CCHMC) will be assessed.

Biochemical Validation. At 6-weeks, we will conduct home visits to: (1) verify abstinence on caregivers who report that they have not smoked in the past 7 days via expired carbon monoxide testing and salivary cotinine (2) obtain

a follow-up salivary cotinine level on children to validate total home smoking bans, and (3) complete assessment of outcomes. Cotinine is generally accepted to be the best of the available biomarkers, with over 95% specificity and sensitivity, it is noninvasive, and easily obtained in young children .[85,86] _ENREF_114 A standard protocol will be used to collect saliva samples from each child at baseline, 6-weeks, and possibly 6 months. Cotinine analyses will be performed with Enzyme Immunoassay techniques by Salimetrics LLC, Sate College, PA. In the child samples, the lower limit of cotinine sensitivity is 0.05 ng/ml (range of sensitivity: 0.06-200 ng/ml); undetectable cotinine values will be recorded as 0 ng/ml.[87,88] Alternatively, if additional funds are available, cotinine analyses may be assessed with liquid chromatography mass spectrometry (LCMS). Caregiver abstinence will be established if the caregiver's expired carbon monoxide level is at or below 6 ppm; salivary cotinine may be assessed to confirm abstinence in caregivers who report they have quit if their exhaled carbon monoxide does not provide verification. At 6 months, we will assess all caregivers via phone or email, and validate self-reported abstinence and total home smoking bans via expired carbon monoxide testing and/or salivary cotinine.

Data Management

Data management will occur at CCHMC. Participants will complete the baseline assessment on a web-enabled tablet research computer. Data will be collected and managed using REDCap (Research Electronic Data Capture).[92] _ENREF_116 The Redcap Mobile App may also be used in order to scan barcodes on samples.

DATA ANALYSIS

Sample Size and Power Estimates

Sample Size. Our estimate of the number of caregivers that we plan to enroll is based on the average number of unique patients and the smoking prevalence of caregivers seen in a 12-month period in the PED at CCHMC. Based on enrollment in previous studies (which had average annual enrollment of 300-350 caregivers), and a 30 month chart review on the number of annual visits for patients with SHS-related complaints (at least 6,000), we are conservatively expecting to enroll 300 caregivers who smoke over 12 months, for a total of 750 caregivers in 30 months. To obtain the effective sample size for power analyses of outcomes, the sample size must be adjusted for potential attrition of approximately 20% at 6 months, although all efforts will be used to decrease this attrition rate, leaving a total of 600; 300 per group.

Estimate of effect sizes: Evaluation of outcomes. Based on the recommendations of Hughes et al.,[85,86] we will use 2 criteria for abstinence: 6-month point prevalence and prolonged abstinence at 6-months. Based on a similar prior study, we expect that 6-month point prevalence in the HHC condition will be 6.3%.[54] For prolonged abstinence, we are basing our estimation on the 2.1% rate for the HHC and 7% rate for SBIRT. We are conservatively estimating a point prevalence cessation rate of 6.3% and prolonged abstinence rate of 2.1% in the HHC group.[54] We are basing our estimate of 6-month point prevalence of the SBIRT group on the odds ratio derived from meta-analyses assessing the effectiveness of NRT vs. a control, ranging from 1.4-4.6,[54] to give a cessation rate of 10-12% in the SBIRT group. However, since a clinical counselor/intake coordinator/research coordinator will be conducting the intervention, we expect high compliance in implementation. Thus, we are estimating a cessation rate of 12% in the SBIRT group. Similarly, for prolonged abstinence, we are assuming a rate of 7% in the SBIRT group.

Power (Table 2). Power analyses are based on estimates of differences in both 6-month point prevalence and 6-month prolonged abstinence between groups. With 300 subjects in each group, we would have 80% power to detect an increase of 6.4% in cessation rate. However, assuming a multiple imputation approach, we would be able to detect a 5.5% increase in cessation rate. For 6-month abstinence, we can detect an increase of 4.5% with 300 subjects per group and 4.2% with the multiple imputation assumption. These estimates are consistent with the predicted cessation rates shown above and published rates.[54,93] For analyses based on regression techniques, using hierarchical linear modeling, sample sizes will be more than sufficient. The effect sizes of interest for these analyses are the correlation

Table 2: Estimated Power for varying sample size

N / group	Odds ratio 80% power-prevalence	Odds ratio 80% power-abstinence	Assumption
300	2.16	3.29	20% loss
375	2.00	3.05	Multiple Imputation

coefficients and squared, semi-partial correlations (squared=incremental R^2). To predict caregiver level variables (Primary Aim 1), with a sample size of 750 and 20% lost to follow-up, we will have >80% power to detect a correlation of 0.11 (r^2=0.013). For examination of smoking bans (Primary Aim 2), these samples sizes would allow us to detect a difference of 12% with 80% power with 300 per group assuming a rate of between 50% and 65% in the HHC group. Using multiple imputation and 375 per group, we could detect a difference of 11% with 80% power.

Analytic Plan

Data analyses will be conducted at CCHMC and at the University of Cincinnati. A DTA will be established with study investigators at the University of Cincinnati. Data will include demographics, smoking behavior, data from the parent assessments, clinical data, and EMR data. The data will be a limited data set stripped of identifiers. It will be shared on an encrypted file.

Preliminary Analyses. Univariate and bivariate examination of variables will be done first. Distributional properties of the continuous outcome variables will be examined. To control for non-normal distributions and heterogeneous error variances, we will use logarithmic transformation and report geometric means and associated 95% confidence intervals; this is particularly relevant for cotinine. We will conduct several preliminary analyses prior to addressing the Study Aims: (1) Examination for out of range values; (2) Comparison of baseline characteristics of caregivers and children across groups. If baseline differences are found, further analyses will include these variables as covariates in assessing caregiver and child outcomes as appropriate; and (3) Attrition analyses to assess if: Participants who were lost to follow-up are different from those retained. Although we do not expect differential attrition by group, it will be evaluated and if it occurs, we will weight the follow-up data to reflect the proportion assigned to each group. If key variables significantly predict attrition, we will examine the analysis with and without the drop-outs. Thus, we will compare our primary outcomes using a multiple imputation approach for missing data to allow maximum utilization of our data. When including those that were lost to follow-up, the outcome data may be weighted using a response propensity analysis[94,95] which uses the baseline distributions on these variables so that follow-up data has the same distributions on these variables as the baseline data. For all analyses we shall include in the model an indicator variable to account for which clinical counselor/intake coordinator/research coordinator was involved in the delivery of the SBIRT or HHC.

General approach for addressing study aims. This is a two-group RCT, wherein caregivers are randomly assigned to the SBIRT Group vs. HHC group. The appropriate statistical models for analyses of data for inclusion of time dependent outcomes are General Linear Mixed Models (GLMM) for data either with a Gaussian/normal distribution or with a binomial or Poisson distribution, using the appropriate link function, invoking Generalized Estimating Equations (GEE) to account for the longitudinal aspect of the data.[96]

We will use GLMM to evaluate the relative effectiveness of the SBIRT versus HHC group on our primary outcomes: point prevalence and prolonged abstinence at 6-months. The analysis will be repeated with caregiver level differences between groups included as covariates. We will use mixed model analysis of covariance, with repeated measures to assess change (controlling for baseline differences between groups) to assess the effect of the SBIRT on secondary outcomes including reduction in use, number of quit attempts, and changes in readiness to quit. Kappa statistic will be used to assess agreement between the caregiver's self-report and the assessment of tobacco use based on expired carbon monoxide levels and/or salivary cotinine at 6 months. It is possible that use of and adherence to the NRT will influence outcomes in the intervention group. In addition, some of the participants in the control condition may obtain NRT during the study interval. We will examine NRT use or dose, defined as self-reported adherence, as a covariate in order to control for this possible relationship.

Analyses for Primary Aims 1-3.

Primary Aim 1, Hypothesis 1: We hypothesize that SBIRT participants will have higher prolonged abstinence and point prevalence cessation rates compared to those in the HHC group. As stated above, our primary approach to the analysis is using multiple imputation, with clinical counselors/intake coordinators/research coordinators included in the model. We shall then use analysis of covariance, to control for any baseline differences of caregivers between conditions. In addition we will also control for motivation to quit, considered a priori as a potential covariate, using the score on the contemplation ladder. As we are stratifying on motivation to quit and caregiver gender, we will initially enter this into the model as an interaction. To address child cotinine as the 6-month outcome, we will use a t-test and then an analysis of covariance to incorporate the variables different at baseline. Incorporating the 6-week outcome values, we will use GLMM invoking GEE for the repeated

measures and also a model including covariates. This approach will be used to assess the intervention's effect on abstinence and point prevalence and child cotinine.

Primary Aim 2, Hypothesis 2: We will evaluate the effectiveness of the SBIRT on total home/car smoking bans and on child SHSe which will be measured by both caregiver report and child salivary cotinine, as recommended by Halterman et al.[87] The reliability of caregiver's reports will be examined by comparing amount of smoking and SHSe levels reported at 6-months using Pearson's correlations. For validation, we will compare the child's salivary cotinine concentrations for those reporting total home/car smoking bans and those not, we shall also examine the change in cotinine levels from baseline for those initiating bans versus not. The computational procedure will use data from the 2 measurement points, controlling for the within-subject correlation of measures repeated over time.[97,98] The main analysis will use GLMM, first to assess the intervention effect alone and then including covariates. First, we will investigate immediate intervention effects based on change from baseline to 6-weeks post-intervention. Next, we will investigate change from 6-weeks to 6-months to examine maintenance effects. To examine overall change, we will use GEE, examining linear and quadratic terms for time, group, and group × time interactions as explanatory variables.[52] Use of NRT, described above, may be of particular interest as a covariate for this analysis.

Primary Aim 3, Hypothesis 3: We hypothesize that the SBIRT intervention effect on prolonged abstinence and point prevalence cessation rates will be mediated by the caregiver's perception of the risk of smoking on their child's health, or on their readiness to quit over time.[42,66,67,69,70,99] Bivariate analyses will be used to initially examine if the variables measuring this phenomena, susceptibility, severity and benefits of quitting are associated with cessation at each time point and if there are any changes in perceived health risk from baseline to 6-months in the SBIRT versus HHC groups. We will build on the models from our primary aim to determine the association of these potential mediators. Analysis assessing these effects will be conducted using abstinence at each follow-up point as the dependent variable and testing for interactions between treatment (i.e., intervention) and the potential mediator. Additionally, we will examine the main effects of the intervention within each level of the mediator to establish whether the intervention is effective in each subgroup, acknowledging that we may be underpowered for some subgroups.

Mediation analysis**:** To assess whether our intervention improved cessation outcomes via the proposed mediators, we will perform mediation analyses using both the criteria of Baron & Kenny[100] and Holmbeck.[101] As our outcome variables are dichotomous, we will apply the method of Huang et al.,[102] which involves a system of logistic regression models and the Monte Carlo method to assess posterior distributions of the direct, indirect, and relative indirect effects. Three sets of logistic regression analyses will be performed, as the variables of interest; outcome, intervention and mediator are mainly categorical. The first 2 steps are to assess the intervention effects on the outcome and the mediator. In the third step, we will assess the relationship between each of the proposed mediators and the study outcome at each follow-up. The same 3 steps will be repeated with adjustment for potential confounders and/or moderators as determined from analysis for Hypothesis 3. The mediating variables that will be considered are: perception of child's risk from SHSe and the benefits to the child of quitting, also motivation to quit, self-efficacy. Moderating variables are household smokers, financial strain, , nicotine dependence, and prior quit attempts.

In the final analysis, the entire theoretical model to predict outcome will be examined using structural equation modeling (SEM). The strength of SEM in examining the entire model is that this method allows for the analysis of a hypothesized pattern of directional and non-directional linear relationships among a set of latent variables (e.g., caregiver beliefs about their child's SHSe risk) and measured variables (e.g., point prevalence).[103] This approach will allow us to examine the effect of perceived risk of SHSe and perceived child benefits of quitting; we will incorporate the former as latent variables over the study period. We will also be able to examine the relative relationship of caregiver's beliefs and readiness to quit with the outcome of cessation.

Analyses for Secondary Aim 1. Working closely with Dr. Laura Akers (health services and economic consultant), we will collect the cost data needed to conduct a cost analysis of the SBIRT intervention. The cost inventory may include costs and charges from the baseline PED visit and hospitalization (if the child is hospitalized) and from SHSe-related PED visits or hospitalizations for the period 6 months before and 6 months after the baseline visit. The cost inventory will also include data collected from CRCs and clinical counselors/intake coordinators/research coordinators in both conditions about cessation-related activities and expenses, self-reported abstinence, and use of all tobacco products at each follow-up. Cost inputs will include staff time for tobacco screening, chart flagging, cessation counseling, giving informational materials and NRT, and referral to the QL, smokefreeTXT, or smokefree.gov. To determine costs of SHSe-related PED visits and hospitalizations

at CCHMC, clinical and cost/charges data will be collected from hospital records for the 6 month period before and after baseline for SHSe-related illness PED visits and hospitalizations such as asthma, and compiling the associated costs We anticipate that the main cost component for intervention delivery will be the minutes the clinical counselors/intake coordinators/research coordinators spends in counseling. Although the intervention will occur during the time the patient is waiting for care, the time the clinical counselor/intake coordinator/research coordinator spends represents an opportunity cost of other alternative ways of spending this time with caregivers and should be tracked for inclusion in the cost-effectiveness analysis. Because the intervention will be delivered during visits of normal length, we do not anticipate that PEDs will incur any other overhead costs (e.g., facilities) due to adoption of the intervention. It is possible that a final version of the SBIRT will require changes in CMS billing codes to accommodate payment for the service. It is premature to determine this now, and establishment of the evidence-base of the intervention is required to provide a justification for a full review of coding options. As we conduct the cost analysis, we will conduct a preliminary review of coding options in anticipation of continued empirical work with the SBIRT to optimize its adoptability in PED settings.

Procedures for Secondary Aim 2. If successful, using the findings from this project and our prior research, we will develop a manual of operations that will enable other PEDs and EDs to adapt and implement the intervention in their setting. Using the CEASE program as a model,[55] this manual of operations will include step-by-step guides with tips and techniques for successful implementation of the intervention. This information will include how to obtain buy-in of policy/decision makers, clinicians, and ancillary staff members, and how to gather information from clinicians and staff on adapting the intervention for use in their site (e.g., taking into account differences in PED patient flow, patient acuity, PED operations, and PED staffing). The manual of operations will also include all provider training materials and intervention guides (e.g., screening for tobacco use, brief intake assessments, instructions on how to give the 3As, motivational interviewing tips, referral resources, and cessation medication prescribing). In addition, we will provide a comprehensive package of patient materials refined during the trial, such as fact sheets (e.g., health effects of SHSe, how to implement a home smoking ban) and cessation referral resources. Finally, we will include all assessments to allow local evaluation of program results.

Analysis for Secondary Aim 3. For the analysis of the CSE study aim, we will calculate descriptive statistics including means, confidence intervals, medians, and interquartile ranges of reported and biochemically measured CSE and SHSe. Logarithmical transformation of the biomarkers may be performed to control for nonnormality and unequal variances. We plan to perform a series of logistic or linear regression models (as appropriate) to assess the associations between reported and biochemically measured CSE and SHSe and child sociodemographics and other characteristics, and household smoking behavior. We will fit linear and logistic regression models (as appropriate) to examine the effect reported and biochemically measured CSE and SHSe has on health effects and healthcare utilization. We will also assess correlations of child SHSe and CSE. We will consider using other appropriate models based on the nature of the data (e.g., fixed effects models, Poisson regression).

Analysis for Exploratory Aim. For our primary goals, we will detect genomic features that distinguish TSE by a 2-fold change with P value < 0.05. For a clinical biomarker, it will be important that there is a large enough effect size to be useful in a clinical setting; thus, our pilot study is powered to give us the data we need to see if any robust effects warrant further study and replication. In addition to our genome-wide analysis, we will especially focus on those loci with significance in previous studies of TSE. Principal component analysis and unsupervised hierarchical clustering will be used to statistically distinguish patients and controls as assessed by a subsequent ROC analysis. Pathway analysis will be performed to identify groups of genes with similar functions or that act in the same biological pathway. We will also specifically evaluate changes in genes found to be altered in previous studies.

CONFIDENTIALITY/SECURITY

All measures will be taken to ensure patient confidentiality. All information will be used for scientific purposes only. Only the primary investigator, co-investigators, and trained study staff will have direct access to

data collected.

All study participants will complete the baseline questionnaire on a web-enabled tablet computer provided by the study. All study data will be collected and managed using REDCap. The CRC will collect the electronic participant surveys and she/he will store them in a secure data center located at CCHMC. Access to the firewalled data by the CCHMC research team is possible only through user specific usernames and passwords. Follow-up surveys will be completed in-person for all caregivers or prompted by a phone call or by an email that will contain a participant specific, REDCap survey link. No identifying information will be contained on the follow-up surveys; surveys will be identified only by an ID number. Timing of caregiver follow-up assessments will be linked to the date of enrollment.

Data safety and monitoring will be managed by the study staff, in accordance with the CCHMC Research Policy for reporting unanticipated events (CCHMC R-18).

The participants will be informed in the consent form regarding limits of confidentiality. Because of the potential legal implications of marijuana use, a Certificate of Confidentiality will be obtained from the U.S. Department of Health and Human Services for this study. Participant confidentiality will be breeched only to protect the safety and welfare of research participants and only in accordance with state and federal law. Participants will be made aware of this policy at the commencement of their involvement in the study.

LOCAL FACILITIES/PERFORMANCE SITES

This research will take place at CCHMC. Participants will be recruited and enrolled in the Emergency Department and/or Urgent Care. The data will be stored and analyzed at CCHMC.

FUNDING PLAN

A grant from the National Institutes of Health/National Cancer Institute (1R01HD083354) was funded with a start date of August 1, 2015.

COMPENSATION

_ENREF_92Payment for follow-up will be as follows:

$20 for completing initial baseline assessment; $10 additional, if a urine sample is obtained.
$20 for completing the 6-week follow-up questionnaire
$30 for completing the 6-week follow-up home/other location visit; $10 additional if a urine sample is obtained;
$30 for completing the 6-month follow-up questionnaire and $35 for completing the 6-month follow-up home/other location visit, if applicable. An additional $10 will be given to participants who provide urine at this visit.

$10 bonus for completing both follow-ups. Completion bonus will be given if participants complete both the six week questionnaire and home visit as well as the 6 month questionnaire and home visit (if applicable).

Additional payments for urine samples will be provided based on the schedule above. This additional incentive is being added to encourage participants to provide urine samples because the rate of collection of urine samples for this study is low. The need to include this additional incentive was not anticipated prior to this point in the study.

METHOD TO BE USED IN PROCURING CONSENT OF SUBJECTS

Caregivers who meet inclusion criteria will be approached by the CRC or investigator. Written informed consent will be obtained from the parent/legal guardian. Parents will be asked if they agree to have any of their child's leftover saliva stored indefinitely for future research. Parents will be asked to initial their consent for this part of the study in the consent form. Assent will be obtained from all children over age 10.

When child participants turn 18 years of age during the course of the study we will attempt to re-consent them until the participant has exceeded the window for the last data collection timepoint. When child participants turn 18 years of age after the study has been completed, we will send them a letter describing the study procedures and give them the option to have their samples that have been stripped of personal identifiers destroyed rather than saved for future research.

DATA SAFETY AND MONITORING PLAN

The DSM Board will consist of individuals with expertise in behavioral research and human subject protection.

The first meeting of the DSM Board for this project would occur shortly after recruitment begins. The first meeting would be devoted to reviewing study protocols, including plans for human subjects, and determining the frequency and content of interim data analyses (if warranted). Subsequent meetings would occur as determined by the DSMB at their first meeting, but will occur at least annually. During these subsequent meetings, the DSMB will evaluate various aspects of the trial, including progress, data quality, recruitment, etc. The DSMB, together with the IRB, will review the rates of adverse events and serious adverse events and provide recommendations to the PI for protocol revision or trial stopping. The PI will inform NIH of any significant action taken as a result of the DSMB finding.

Frequency of DSM Reviews

The Principal Investigator will monitor the data safety and efficacy of this trial on an on-going basis, implementing the Data and Safety Monitoring Plan (DSMP), and complying with the reporting requirements. The IRB or DSM Board may request more frequent reviews (based on reported Adverse Events or Serious Adverse Events or for other reasons), with which Dr. Mahabee-Gittens will comply.

Collection and Reporting of AEs and SAEs

For purposes of monitoring and reporting adverse events, the following NIH definitions will be used: “Adverse event (AE): Any untoward medical occurrence that may present itself during treatment or administration of an intervention, and which may or may not have a causal relationship with the treatment.” “Serious adverse event (SAE): Any medical occurrence that results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; creates persistent or significant disability/incapacity, or a congenital anomaly/birth defects.”

We do NOT anticipate any SAEs to be reported as a result of participation in this study. If a subject experiences any AEs/SAEs as a result of this study, all study staff will be trained by the PI to report these events to their CRC or use the toll-free phone number to contact the PI or the IRB at CCHMC directly within 24 hours of report of the event. If an AE or SAE is reported to the CRC, the CRC must report the event to the PI within 24 hours of notification. Patients may report AEs or SAEs directly to CCHMC via a local phone number available in their copy of the consent form.

The PI will report any AEs/SAEs to the CCHMC IRB within 24 hours of receipt of report from any source. AEs and SAEs will be reviewed by the IRB and/or the DSMB in a timely manner (depending on the severity of the event). All AEs and SAEs will be reported to NIH at a minimum in the annual progress report, or within 24 hours depending on the severity of the event.

Reporting Mechanisms of AEs/SAEs to the IRB, FDA, and NIH

All study CRCs will be trained to report any adverse event regarding patients enrolled in the study. These events would include severe withdrawal symptoms, reaction to use of nicotine replacement products, severe illnesses or death (from any cause).

Study staff may contact the PI in person, or the IRB at CCHMC directly within 24 hours of report of the event. If an AE or SAE is reported to the CRC, the CRC must report the event to the PI within 24 hours of notification.

Caregivers may report AEs or SAEs to the PI either in person or using the local study number to contact the PI or IRB at CCHMC directly. The Principal Investigator will report any AEs/SAEs to the CCHMC IRB within 24 hours of receipt of report from the subject. AEs and SAEs will be reviewed by the IRB and/or the DSMB in a

timely manner (depending on the severity of the event). All AEs and SAEs will be reported to NIH at a minimum in the annual progress report, or within 24 hours depending on the severity of the event.

Reporting Mechanisms of IRB Actions to NIH

Any IRB action that results in stopping or significantly altering the trial will immediately be reported (within 24 hours of notification) to NIH by the CCHMC IRB Administrator.

Report of Changes or Amendments to the Protocol

The Principal Investigator will report and seek approval of the CCHMC IRB for any changes to the study protocol. A significant alteration of the study protocol will be reported to NIH by the IRB Administrator immediately.

FDA Regulated Research

Nicotine, an FDA-approved drug, does not require an Investigation New Drug (IND) application with the FDA, as the use in the current research is consistent with currently approved indications by the FDA.

APPENDICES

Appendix A: (Baseline Assessment): Intervention to Reduce SHSe

Appendix B: SBIRT Materials

Appendix C: HHC Materials

Appendix D: Caregiver Locator and Demographic Screener

Appendix E: Eligibility Screener

Appendix F: NRT Checklist and Receipt Documentation

Appendix G: Six Week Assessment

Appendix H: Six Month Assessment

Appendix I: NRT Checklist and Receipt Documentation- 6 Weeks

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