HHS Public Access

Author manuscript

Contemp Clin Trials. Author manuscript; available in PMC 2018 September 12.

Published in final edited form as:

Contemp Clin Trials. 2018 September ; 72: 1–7. doi:10.1016/j.cct.2018.07.008.

Nicotine replacement therapy sampling via primary care: Methods from a pragmatic cluster randomized clinical trial⋆

Jennifer Dahne[a,c,*], **Amy E. Wahlquist**[b,c], **Amy S. Boatright**[a,c], **Elizabeth Garrett-Mayer**[b,c], **Douglas O. Fleming**[d,e], **Robert Davis**[d,f], **Brent Egan**[d,f], and **Matthew J. Carpenter**[a,b,c,**]

[a]Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina (MUSC), Charleston, SC, USA

[b]Department of Public Health Sciences, MUSC, Charleston, SC, USA

[c]Hollings Cancer Center, MUSC, Charleston, SC, USA

[d]Care Coordination Institute, Greenville, SC, USA

[e]Spatial Sciences Institute, University of Southern California, Los Angeles, CA, USA

[f]School of Medicine, University of South Carolina Greenville, Greenville, SC, USA

Abstract

Background: Primary care is the most important point of healthcare contact for smokers. Brief physician advice to quit, based on the 5As/AAR model, offers some efficacy but is inconsistently administered and has limited population impact. Nicotine replacement therapy (NRT) sampling, defined as provision of a brief NRT starter kit, when added to the 5As/AAR, is well-suited to primary care because it is simple, brief, and can be provided to all smokers. This article describes the design and methods of an ongoing comparative effectiveness trial testing standard care vs. standard care + NRT sampling within primary care.

Methods: Smokers were recruited directly from primary care practices between July 2014 and December 2017 within an established network of South Carolina clinics. Interventions were delivered randomly by clinic personnel, and phone-based follow-ups were centrally coordinated by research staff to track outcomes through six months post-intervention. Primary study aims are to examine the impact of NRT sampling on smoking, inclusive of cessation, quit attempts, and uptake of evidence-based treatment.

Results: Twenty-two clinics were recruited. Across clinics, patient census ranged from 985 to 10,957 and number of providers ranged from 1 to 63. Average patient age across clinics was 52.9 years and smoking prevalence across ranged from 10.6% to 28.5%.

Conclusion: Improving the effectiveness and reach of brief interventions within primary care could have a considerable impact on population quit rates. We consider the advantages and

*Correspondence to: J. Dahne, Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, 67 President Street, MSC 861, Charleston, SC 29425, USA. dahne@musc.edu. **Correspondence to: M. J. Carpenter, Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, 86 Jonathan Lucas Street, Charleston, SC 29425, USA. carpenter@musc.edu.

disadvantages of key methodological decisions relevant to the design of future primary care-based cessation trials.

Keywords

Smoking cessation; Primary care; Nicotine replacement therapy

1. Introduction

Despite recent advances in the treatment of tobacco dependence, smoking and tobacco use continue to be the leading cause of preventable mortality [1]. The primary care setting is a powerful venue through which to identify large numbers of smokers and engage them in quitting as at least 70% of smokers visit a primary care physician (PCP) annually [2]. US Public Health Service (USPHS) clinical practice guidelines advise the 5As model (Ask, Advise, Assess, Assist, Arrange) or its revised alternative (Ask, Advise, Refer) for primary care cessation treatment [3]. However, compliance with this model is modest [4–11]. Typical obstacles at the provider level include lack of familiarity with guidelines, lack of confidence to counsel cessation, inadequate knowledge or skills, and lack of time [12–15]. Thus, PCPs need more and better tools to treat smokers. Any such strategies, if they are to be truly adopted, need to be brief, easy to implement, and noninvasive of either clinic procedures or doctor/patient dialogue of other medical issues.

Despite the evidence base in support of cessation medications, only 29%–38% of smokers who make a quit attempt use them [16, 17]. The most widely used cessation medication is nicotine replacement therapy (NRT), with over the counter NRT formulations (nicotine patch, gum, lozenge) offering the greatest potential for widespread population dissemination. Meta-analytic evidence from 100+ trials shows a doubling of long-term abstinence [3, 18] associated with NRT and significant reductions in withdrawal and craving [19, 20]. NRT sampling refers to providing short starter packs of NRT and is distinct from a full course of treatment in that the intent is to engage smokers in the process of quitting without any requirement or expectation to quit immediately/ abruptly. As NRT sampling is a pragmatic, low intensity, low cost intervention that takes less than one minute to implement, it could easily be added to existing AAR protocols within primary care.

Our team has conducted one prior randomized clinical trial (N = 849), not within primary care, testing the concept of NRT sampling to induce cessation behavior among smokers unmotivated to quit [21, 22]. Smokers were recruited nationally and randomized to either 1) NRT sampling, within the context of a practice quit attempt (PQA), or 2) PQA alone. Uptake of NRT during the sampling period was high, with 73% of smokers using the product, for an average of nine days. Cessation outcomes were also promising. NRT sampling compared to PQA alone was associated with a significantly higher incidence of any quit attempt (49% vs 40%; relative risk [RR], 1.2; 95% CI, 1.1–1.4) and any 24-h quit attempt (43% vs 34%; RR, 1.3; 95% CI, 1.1–1.5) and was marginally more likely to promote “floating abstinence” (i.e., seven days without smoking at any point during the study; 19% vs 15%; RR, 1.3; 95% CI, 1.0–1.7) [22].

We now extend NRT sampling to primary care, in addition to standard care (AAR models), believing it to be uniquely advantageous in this setting because it 1) takes 1–2 min to implement, 2) can be utilized with all smokers regardless of motivation to quit, 3) requires no substantive training of clinicians, and 4) is a concrete behavioral exercise that smokers and providers can "hang their hat on." We herein describe the design and methodology of Tobacco Intervention in Primary Care Treatment Opportunities for Providers (TIP TOP), a large, ongoing comparative effectiveness trial (Clinical Trials Registration Number NCT02096029) to further test NRT sampling, with a primary focus on abstinence.

2. Methods

2.1. Overview of design and study hypotheses

Within a multi-site, cluster randomized clinical trial, smokers were randomized to 1) standard care (Ask, Advise, Refer) or 2) standard care + NRT sampling. Site and participant enrollment occurred from July 2014 through December 2017, and follow-up assessments were completed in June 2018. Twenty-two primary care clinics across South Carolina were enrolled in the trial. Randomization was at the clinic level, but the unit of analysis is the individual smoker. Following consent, baseline assessment, and provider intervention (all done within clinic during routine visits), follow-up phone assessments occurred at one, three, and six months intervals. The primary study outcome will be seven-day point prevalence abstinence (PPA) at the six-month follow-up assessment. Secondary outcomes include incidence/duration of quit attempts, smoking reduction, and utilization of cessation treatment resources. We hypothesize that, as compared to standard care, standard care + NRT sampling within the primary care setting will result in: 1) higher incidence of PPA at six months, 2) a longer period of abstinence across the entire study duration, 3) higher rates of quit attempts, and 4) higher uptake of evidence-based cessation treatment. We further hypothesize that these effects will be mediated by increases in: 1) abstinence self-efficacy, 2) motivation to quit, 3) positive attitudes toward NRT use, and 4) autonomy in quitting.

2.2. General recruitment method, clinic eligibility, and participant eligibility

2.2.1. Recruitment method—Participants were recruited directly within their usual primary care settings during routine visits (i.e., not dedicated for this study). We partnered with Care Coordination Institute, LLC (CCI; https://www.ccihealth.org) which offers a network of ~120 clinic sites across South Carolina, inclusive of > 7500 providers and 1.3 million patients. Each clinic was asked to enroll participants proportional to the demographics of their clinic (e.g., if a clinic's census consisted of 65% White patients, we asked that they recruit a similar proportion of White participants into the study).

2.2.2. Clinic eligibility—Clinics considered for study inclusion were located within the state of South Carolina and had a census of approximately 1000 patients or more. Veterans Administration Health Care System clinics and major teaching hospitals were excluded. From these criteria, a list of 70 potential sites was generated, and 20 clinics were chosen based on clinician interest and recommendations from CCI staff. Five clinics declined participation upon invitation and alternate clinics were selected from the list of potential sites. Target participant enrollment for each clinic was 58 participants within a three-month

enrollment period, though clinics were invited to enroll up to 68 participants (see sample size estimations below). Participating clinics were compensated for their time and effort based on enrollment into the study and number of participants enrolled.

2.2.3. Participant eligibility—Participant-level inclusion criteria were kept broad to maximize a population-based focus. These included: 1) age 18+, 2) smoker of at least five cigarettes per day on ≥25 days out of the last 30 days, 3) English speaking, and 4) recruited through a primary care site actively enrolled in the study. Exclusion criteria included FDA contraindications for NRT use, specifically: 1) current pregnancy, breastfeeding, or planning to become pregnant and/or 2) cardiovascular trauma within the last three months. Motivation to quit smoking was not required.

All in-clinic study procedures were conducted with study participants by IRB-approved clinic staff (e.g., nurses, physicians' assistants) and took place during routine clinic visits. Clinic staff identified smokers using the clinic's Electronic Medical Record (EMR), elicited interest from potential participants, and screened those most likely to be eligible/interested. If interested, a study recruiter completed an eligibility assessment, with all data entered into REDCap [23], a HIPAA-compliant online database. Eligible participants completed informed consent with this same clinic recruiter, and all consent forms were mailed to the research study team. After completing informed consent, participants completed a baseline questionnaire packet in clinic (also entered into REDCap). The baseline questionnaire was intentionally kept brief to minimize burden on clinical staff during patient visits and included information on basic demographics, nicotine dependence, prior quit attempts, and quit methods used.

2.3. Interventions

2.3.1. Standard care—A key decision point for this trial was the amount of intervention that should be provided to the control group. Our priorities here were to maximize external validity and minimize the amount of additional training provided to clinicians across both standard care and NRT sampling interventions. To maximize external validity, the standard care treatment should mimic as closely as possible the usual practice for smoking cessation within primary care. As such, we based our standard care intervention on the AAR model and provided clinicians in both the standard care and NRT sampling conditions with a brief AAR training prior to study initiation. Bachelors level study staff with Tobacco Treatment Specialist (TTS) training delivered an in-clinic, in-person, 60–90 min training to both provide a standardized overview of AAR recommendations as well an overview of study procedures. We emphasized that providers could counsel their smokers as they normally would. As per AAR recommendations, counseling might include a brief discussion of the risks of smoking and benefits of quitting, advice on effective strategies for smoking cessation (including use of pharmacotherapy), and referrals to the state quitline. Videos were created and distributed for any clinic staff who wanted to review this material. A small packet was provided to all participants that included information on quitting smoking, FDA-approved cessation medications, and the state quitline. The packet also contained information on reaching the central study staff (toll-free number) and the study follow-up

assessment schedule. To make the active and control treatments more equal, standard care participants were provided with a roll of mints in their take-home packet.

2.3.2. Standard care + NRT sampling—Clinics randomized to the standard care + NRT sampling condition provided NRT samples to study participants in addition to all standard care treatment previously described. Providers could discuss the products to the extent they felt comfortable, with an emphasis on product safety and efficacy, again with rationale to keep this as naturalistic as possible. Detailed information on each product, including instructions for use, were provided in the same take-home packet which also included frequently asked questions and related information intended to dispel medication misperceptions.

Participants were provided with a two-week supply of both nicotine lozenge and patch, both in the original packaging, in uniform dosages (14 mg patch, 4 mg lozenge in cherry flavor). We considered a tailored dosing to higher dependence levels (e.g., with 21 mg patch) but believe 1) this diminishes the translational potential of this intervention, and 2) that it is not clinically indicated given the adjunctive use of lozenge. We provided 4 mg lozenges rather than 2 mg lozenges to prevent underdosing those who would choose to use only one NRT product. Lozenge flavor was limited to cherry to reduce heterogeneity across participants. We selected a two-week duration of NRT for several reasons. Few smokers visit their PCP more than once within a six-month window (the study duration). Thus, the NRT sampling intervention needed to be based within a single office visit. We considered a longer duration of NRT sampling or providing participants with repeated sampling opportunities (e.g., a new sample provided every X weeks). However, we believed this modification would undermine the intent of a brief intervention. Whereas two weeks of sampling might be something that clinics (or insurance companies) are willing to support, more sustained provision of free medication would be unlikely, particularly as applied here to a broad spectrum of smokers.

2.4. Follow-up procedures

Following study enrollment during their primary care visit, participants received a reminder call within three days to remind them of study involvement and the schedule of follow-up assessments. All subsequent follow-ups occurred over the phone, with each follow-up phone call lasting approximately 15 min. All participants were compensated for completion of study follow-up assessments via gift cards mailed to their home address.

2.5. Patient-level outcomes

Measures included in this trial were selected based on precedent, with the goal to remain consistent with our prior trial of NRT sampling [22].

2.5.1. Smoking abstinence, incidence/duration of quit attempts, and smoking reduction—Using a modified timeline followback procedure [24] at each follow-up phone call, participants self-reported number of days smoked and incidence/duration of quit attempts since the last assessment. Our primary study outcome is PPA at the six-month follow-up assessment, defined as self-report of not smoking at all for seven consecutive days. We use this definition of PPA because it is the Society for Research on Nicotine and

Tobacco (SRNT) workgroup's recommended outcome for "cessation-induction" studies that use interventions to prompt quitting in which the effect of the intervention may be delayed and/or there is not a set quit date [25, 26]. Additional outcomes based on timeline followback data include longest duration of abstinence and continuous abstinence since the baseline visit.

2.5.2. Utilization of cessation treatment resources—We determined the amount and frequency of NRT used (per product) and determined use of provided products (lozenge + patch) vs. additional purchase of products at each follow-up assessment. At the first follow-up, we also queried about receipt of specific 5As components. Participants were specifically asked to report, in reference to their last office visit, whether their physician or other healthcare provider: 1) asked about smoking status, 2) advised quitting smoking, 3) asked about willingness or readiness to quit smoking, 4) discussed medications for quitting, 5) advised medication use to quit smoking, 6) provided medication to quit smoking, and 7) provided a referral to the state smoking cessation quitline. These items could be used to determine whether the NRT sampling protocol was uniformly implemented across clinics.

2.5.3. Potential treatment mediators—At each follow-up assessment, participants completed assessments of cessation self-efficacy, motivation to quit, attitudes toward NRT, and quitting autonomy. Self-efficacy was assessed via a one-item measure of confidence in remaining quit over the next month and motivation to quit was assessed using a modified contemplation ladder to measure motivation to quit in the next month [27]. Attitudes toward NRT were assessed using a two item scale that queried for concern about the safety of NRT products and beliefs that NRT products improve a smoker's chance of quitting successfully [22]. This scale was abbreviated from the scale used in our prior trial of NRT sampling, which utilized eight items to assess positive attitudes toward NRT and four items to assess negative attitudes toward NRT. Quitting autonomy was assessed using the Treatment Self-Regulation Questionnaire [28, 29], a well-established measure of autonomous motivation (i.e., the degree to which decisions on quitting are self-determined and/or controlled by others).

2.6. Provider- and clinic-level outcomes

In addition to patient-level study outcomes listed previously, secondary study outcomes include those at both the provider- and clinic levels. Participating providers at all enrolled clinics were e-mailed a brief survey prior to study enrollment and within one week of the site's completion to assess attitudes toward and practices of tobacco dependence treatment. Providers were not compensated specifically for the completion of these assessments, but each clinic was compensated for participation in the trial. This assessment included questions related to provider demographics, beliefs about tobacco cessation treatment via primary care, knowledge of cessation treatments and resources, confidence in treating tobacco dependence, frequency of 5A's administration, barriers to provision of the 5A's, and feedback related to participation in the trial. Provider report of frequency of 5A's administration and patient self-report of receipt of the 5A's can be utilized to determine the intensity of the standard care intervention. In addition, our partnership with CCI allowed us to collect aggregate data on the clinic level including the numbers of tobacco-related

insurance claims and smokers within each clinic. Those data were collected from the electronic medical record for each participating clinic for discrete periods prior to, during, and following trial involvement. With these data, we can secondarily examine whether study involvement leads to clinic-wide changes in tobacco cessation treatment and whether such changes vary as a function of clinic treatment condition.

2.7. Sample size estimation

2.7.1. Expected abstinence rates—The primary outcome on which our study is powered is seven-day point prevalence abstinence at the six-month follow-up assessment [30]. Based on prior published effect sizes for interventions similar to AAR [3, 30, 31], we conservatively estimated a base rate of 13% abstinence in the standard care group. To estimate an effect for the NRT sampling condition, we identified studies comparable to ours that provided brief samples of NRT. This literature is primarily based on quitline studies (which also give out brief samples of NRT), among smokers motivated to quit. These quit estimates ranged from 15.6% to 34% [27, 32, 33]. We also drew from our prior work with 426 exclusively unmotivated smokers in which we found a 16% quit rate [22]. From these collective estimates, we erred on the lower range and estimated that 20% of smokers in the NRT sampling group would achieve abstinence at six-month follow-up assessment.

2.7.2. Intraclass correlation (ICC)—We expected some degree of intra-clinic (i.e., intraclass) correlation, which may impact study outcomes. We used data from previous studies [22, 34] to estimate an ICC of 0.005 based on the variance of abstinence rates across the population. A standard comparison of proportions was used to estimate the sample size, and then inflated using a standard approach for group-randomized trials: $n_c = 1 + (n - 1)ICC$ where n is the number of patients per clinic if no clustering exists and nc is the inflated estimate based on an assumed positive value of ICC. We then calculated sample size estimates based on the number of clinics chosen, with estimates using a presumed abstinence rate of 13% vs. 20% in standard care vs. NRT sample group, ICC = 0.005, power = 0.80, and alpha = 0.05. Final planned enrollment was 20 total clinics with each clinic recruiting a minimum of 58 participants, for a total planned enrollment of 1160 participants.

2.8. Data analytic plan

All forthcoming analyses will be based on an intent-to-treat approach. Any significant baseline differences between groups will be included in analyses. Missing values will be imputed as if the participant made no quit attempts and returned to baseline levels of smoking. This conservative approach biases all results toward the null hypothesis. Logistic regressions will then be used for each binary outcome with treatment group (standard care vs. NRT sampling) as the covariate, estimated using generalized estimating equations (GEE) to account for clustering within clinic. Rates for each outcome will be estimated along with 95% confidence intervals and statistical significance will be evaluated using Wald tests at one-sided 0.025 level. For continuous outcomes, such as duration of abstinence, a linear regression framework will be used in the GEE models.

3. Results

See Table 1 for clinic-level demographic data for the enrolled clinics. During the course of recruitment, two clinics (both randomized to the standard care condition) fell below the target enrollment pace. Participants from these two clinics are included in the final study sample but the clinics themselves were subsequently replaced. Thus, 22 clinics joined the study in all. Across clinics, the total patient census ranged from 985 to 10,957 patients and the total number of medical providers per clinic ranged from 1 to 63. Average patient age across clinics was 52.9 years. We report clinic-level smoking prevalence for those clinics in which at least 75% of patients were queried for smoking status as indicated in the electronic medical record. Using these data, smoking prevalence across clinics ranged from 10.6% to 28.5%.

Enrollment with the first clinic began in July 2014, and the final clinic completed its enrollment target in December 2017. Follow-up data collection was completed in June 2018 and main outcomes are forthcoming. We opt not to include baseline characteristics of our final study sample here because those data are better suited to accompany the main outcomes of the trial.

4. Discussion

As noted in the USPHS clinical practice guidelines, new research examining cessation treatments must be conducted within real-world clinical settings [3]. This study does exactly that. More intensive treatments, even within primary care settings, are likely more effective than the brief interventions tested herein [35–37]. However, sustaining such interventions after completion of a study is questionable. NRT sampling takes a less intensive approach, offering pragmatic, translational appeal. Moreover, NRT sampling is applicable and may be effective in all groups of smokers, including those not initially motivated to quit. Time- and skill-intensive treatments do not easily lend themselves to implementation within busy clinical practices, where the median caseload per clinician often exceeds 2000 [38] and the average length for each visit is 20–23 min [39, 40]. In fact, estimates indicate that a PCP would spend 21.7 h daily to deliver evidence-based care for all patients in a typical caseload [38].

With this trial design, our team has efficiently recruited a geographically diverse sample of smokers across the state of South Carolina via their primary care clinics. Similar trial designs may be useful for future studies of smoking cessation treatments within primary care. In addition to methodological issues discussed earlier, we consider here the advantages and disadvantages of key methodological decisions that may be relevant to the design of future cessation trials within primary care.

4.1. Randomization at the clinic vs participant level

We considered randomizing participants at the individual rather than at the clinic level but ultimately opted against this approach due to concern regarding within-provider and within-clinic contamination of treatment effects. This, in turn, necessitated enrolling enough clinics to have sufficient statistical power and sample heterogeneity while also remaining mindful

of study feasibility. Enrolling more clinics would increase sample heterogeneity, but would also increase study workload, both in terms of clinician training and site management. We balanced the need for statistical power and sample heterogeneity with study feasibility by enrolling 22 clinics with an achievable number of participants within each. A byproduct of randomization at the clinic level is that there may be demographic differences between participants randomized to each group, if only because participant demographics tend to be nested within clinics. For example, the two clinics with the highest prevalence of Black patients were both randomized to the standard care condition. We attempted to mitigate this by balancing the number of small, large, urban, and rural clinics enrolled, although these designations have their own limitations since clinic size can change rapidly due to acquisitions and clinic mergers. In the future, an additional way to mitigate this issue would be to stratify randomization based on clinic demographics (e.g., patient race/ethnicity, gender, average age).

4.2. Biological verification of abstinence

We opted not to impose biological verification of abstinence (e.g., via breath carbon monoxide or urinary/salivary cotinine) throughout the study follow-up period. We made this decision for a number of reasons. First, the SRNT guidelines [30] for minimal intervention studies (1–3 min herein) suggest that biological verification is not necessary. Second, we believe that demand characteristics are minimized through independent follow-up assessment with study research staff that are not affiliated with the participant's primary care clinic. Third, in trying to keep this study as "real-world" as possible, we do not believe the real-world scenario is that PCPs would collect biological verification of smoking behavior. Fourth, when the study began, remote verification of smoking abstinence was difficult, but not impossible, and typically consisted of requiring participants to mail urine or saliva samples for cotinine testing to the research team. In the time since the study began, other more feasible methodologies have been developed to remotely capture CO, such as having participants video record themselves providing a CO sample and/or utilizing a CO monitor that connects to a smartphone [41–44]. These remote CO capture procedures may help facilitate biological verification of abstinence in similar future studies designed to assess treatment efficacy.

4.3. Balancing pragmatism with depth

Across both standard care and NRT sampling interventions, we sought to minimize disruptions to clinic flow. We relied on clinic staff to recruit participants and implement the interventions. Alternative approaches, such as embedding research staff into each clinic [45], may have increased the pace of participant recruitment but also would have decreased the translational nature of the trial. Our hands-off approach limited the depth of our clinic procedures, particularly surrounding the scope of baseline assessments. This approach also meant that we could not ensure consistency and fidelity of interventions across clinics and over time. However, a hands-on approach is not sustainable for real world implementation, which was our guiding philosophy. Because we mimicked real world treatment practices as closely as possible, we hope that if NRT sampling proves efficacious within this trial, the intervention will easily be able to be translated from this research study into clinical practice.

Consideration of clinic flow and the impact of a smoking cessation intervention on standard operating procedures within a primary care clinic is a key consideration at the outset of any primary-care based smoking cessation trial. In this trial, we sought to minimize disruptions to clinic flow by embedding research procedures into routine clinic appointments for any presenting complaint, rather than requiring a dedicated patient appointment for this study. There may be other methods that would further minimize clinic disruption. For example, automated alerts can be built into the EMR to prompt providers to screen patients for study eligibility within a portal already utilized by the clinic. The EMR could also be utilized to send patients screening surveys prior to their scheduled medical appointment so that limited in-clinic time is not dedicated to completion of study procedures. These and other recruitment/enrollment options could be discussed with clinic staff prior to study onset to determine the best ways to minimize clinic disruption while also promoting study enrollment.

4.4. Motivation to quit

All smokers, regardless of motivation to quit, were study eligible. We decided to include all comers because NRT sampling has unique benefits to unmotivated smokers, as our prior research demonstrates [21, 22]. We also believe that NRT sampling will be beneficial to smokers who do want to quit, essentially serving as a starter kit for abstinence (akin to quitline callers). Sensitivity analyses can assess if treatment effects are specific to those with high vs. low desire to quit. If NRT sampling were to be fully implemented within clinic practice, it is unlikely that physicians would provide samples to specific groups of smokers only, as this would add additional burden to intervention delivery. In fact, some studies suggest that the simple provision of free medication can alter the distribution of smokers' motivation to quit [46].

4.5. Consent for study enrollment

Consent for study enrollment was completed in clinic with an IRBapproved member of the clinic's staff. The same consent form and consenting procedures were used across clinics. Only participants who could read the consent form were included in the study. The completed consent form was then mailed to research staff to complete each participant's enrollment. This process required all clinic staff facilitating consent to complete necessary research ethics trainings (e.g., CITI training) to become IRB-approved consenters. For each clinic, this process took approximately four to six weeks. Other options to consent research participants have become available since this study began, and these may have reduced study burden on clinic staff while also facilitating more efficient clinic enrollment. For example, video consent via a HIPAA-compliant service such as doxy.me [47] or electronic consent via REDCap paired with a phone call would allow each participant to be connected in real time to an offsite member of the research team to complete consent. This procedure likely would decrease burden on inclinic staff. Video consent and similar procedures (e.g., electronic consent, telephone consent) may improve the feasibility of similar trial designs in the future.

4.6. Significance

In sum, the primary care setting represents a unique opportunity to engage smokers in quitting. In an era when most intensive treatments do not lend themselves to real-world

implementation, NRT sampling represents a brief, concrete, easy to explain strategy that has strong empirical and theoretical support, and thus offers both clinical and policy significance. The methods of this comparative effectiveness trial are strengthened by 1) a large sample size, 2) proactive recruitment in real-world settings, 3) an intervention that is simple, face valid, and incurs minimal time intrusion on clinical practice, 4) strong infrastructure to ensure timely recruitment and optimal rates of participant retention, and 5) multiple measures of outcome. We believe this study will offer an important contribution to the literature and considerable implications for smoking cessation.

Acknowledgments

☆ Funding for this research was provided by NIDA grants R01 DA021619, T32 DA007288, and K23 DA045766. Clinical Trials Registration Number NCT02096039.

References

[1]. US Department of Health and Human Services, The health consequences of smoking—50 years of progress, A Report of the Surgeon General Atlanta, GA, 2014.

[2]. Jamal A, Dube SR, Malarcher AM, et al., Tobacco use screening and counseling during physician office visits among adults—national ambulatory medical care survey and national health interview survey, United States, 2005–2009, Morb. Mortal. Wkly Rep 61 (2012) 38–45.

[3]. Fiore MC, Jaen CR, Baker TB, et al., Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline, US Public Health Service, Rockville, MD, 2008.

[4]. Chase EC, McMenamin SB, Halpin HA, Medicaid provider delivery of the 5A's for smoking cessation counseling, Nicotine Tob. Res 9 (2007) 1095–1101. [PubMed: 17978983]

[5]. Browning KK, Ferketich AK, Salsberry PJ, Wewers ME, Socioeconomic disparity in provider-delivered assistance to quit smoking, Nicotine Tob. Res 10 (2008) 55–61. [PubMed: 18188745]

[6]. Blumenthal DS, Barriers to the provision of smoking cessation services reported by clinicians in underserved communities, J. Am. Board Family Med 20 (2007) 272–279.

[7]. An LC, Bernhardt TS, Bluhm J, et al., Treatment of tobacco use as a chronic medical condition: primary care physicians' self-reported practice patterns, Prev. Med 38 (2004) 574–585. [PubMed: 15066360]

[8]. Denny CH, Serdula MK, Holtzman D, Nelson DE, Physician advice about smoking and drinking: are US adults being informed? Am. J. Prev. Med 24 (2003) 71–74. [PubMed: 12554026]

[9]. Cabana MD, Rand CS, Powe NR, et al., Why don't physicians follow clinical practice guidelines? JAMA 282 (1999) 1458–1465. [PubMed: 10535437]

[10]. Blumenthal DS, Barriers to the provision of smoking cessation services reported by clinicians in underserved communities, J. Am. Board Fam. Med 20 (2007) 272–279. [PubMed: 17478660]

[11]. Garg A, Serwint JR, Higman S, et al., Self-efficacy for smoking cessation counseling parents in primary care: an office-based intervention for pediatricians and family physicians, Clin. Pediatr 46 (2007) (252–7).

[12]. Papadakis S, McDonald P, Mullen K-A, Reid R, Skulsky K, Pipe A, Strategies to increase the delivery of smoking cessation treatments in primary care settings: a systematic review and meta-analysis, Prev. Med 51 (2010) 199–213. [PubMed: 20600264]

[13]. Kruger J, O'Halloran A, Rosenthal A, Assessment of compliance with US public health service clinical practice guideline for tobacco by primary care physicians, Harm Reduct. J 12 (2015) 7. [PubMed: 25889679]

[14]. Kruger J, O'Halloran A, Rosenthal AC, Babb SD, Fiore MC, Receipt of evidence based brief cessation interventions by health professionals and use of cessation assisted treatments among current adult cigarette-only smokers: National Adult Tobacco Survey, 2009–2010, BMC Public Health 16 (2016) 141. [PubMed: 26868930]

[15]. Schnoll RA, Rukstalis M, Wileyto EP, Shields AE, Smoking cessation treatment by primary care physicians: an update and call for training, Am. J. Prev. Med 31 (2006) 233–239. [PubMed: 16905034]

[16]. Babb S, Malarcher A, Schauer G, Asman K, Jamal A, Quitting smoking among adults—United States, 2000–2015, Morb. Mortal. Wkly Rep 65 (2017) 1457–1464.

[17]. Dahne J, Wahlquist AE, Garrett-Mayer E, Heckman BW, Cummings KM, Carpenter MJ, State tobacco policies as predictors of evidence-based cessation method usage: results from a large, nationally representative dataset, Nicotine Tobacco Res (2017) ntx192.

[18]. Silagy C, Lancaster T, Stead L, Mant D, Fowler G, Nicotine replacement therapy for smoking cessation, The Cochrane Database of Systematic Reviews, 3 ed., 2004.

[19]. West R, Shiffiman S, Effect of oral nicotine dosing forms on cigarette withdrawal symptoms and craving: a systematic review, Psychopharmacology 155 (2001) 115–122. [PubMed: 11400998]

[20]. Molander L, Lunell R, Fagerström KO, Reduction of tobacco withdrawal symptoms with a sublingual nicotine tablet: a placebo controlled study, Nicotine Tob. Res 2 (2000) 187–191. [PubMed: 11072457]

[21]. Carpenter MJ, Alberg AJ, Gray KM, Saladin ME, Motivating the unmotivated for health behavior change: a randomized trial of cessation induction for smokers, Clin. Trials 7 (2010) 157–166. [PubMed: 20338901]

[22]. Carpenter MJ, Hughes JR, Gray KM, Wahlquist AE, Saladin ME, Alberg AJ, Nicotine therapy sampling to induce quit attempts among smokers unmotivated to quit: a randomized clinical trial, Arch. Intern. Med 171 (2011) 1901–1907. [PubMed: 22123796]

[23]. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG, Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support, J. Biomed. Inform 42 (2009) 377–381. [PubMed: 18929686]

[24]. Sobell L, Sobell M, Timeline Followback User's Guide: A Calendar Method for Assessing Alcohol and Drug Use, Addiction Research Foundation, Toronto, 1996.

[25]. Hall SM, Humfleet GL, Muñoz RF, Reus VI, Prochaska JJ, Robbins JA, Using extended cognitive behavioral treatment and medication to treat dependent smokers, Am. J. Public Health 101 (2011) 2349–2356. [PubMed: 21653904]

[26]. Hughes JR, Keely JP, Niaura RS, Ossip-Klein DJ, Richmond RL, Swan GE, Measures of abstinence in clinical trials: issues and recommendations, Nicotine Tob. Res 5 (2003) 13–25. [PubMed: 12745503]

[27]. Fellows JL, Bush T, McAfee T, Dickerson J, Cost effectiveness of the Oregon quitline "free patch initiative", Tob. Control 16 (Suppl 1) (2007) i47–i52. [PubMed: 18048632]

[28]. Williams GC, Gagne M, Ryan RM, Deci EL, Facilitating autonomous motivation for smoking cessation, Health Psychol 21 (2002) 40–50. [PubMed: 11846344]

[29]. Williams GC, McGregor HA, Sharp D, et al., Testing a self-determination theory intervention for motivating tobacco cessation: supporting autonomy and competence in a clinical trial, Health Psychol 25 (2006) 91–101. [PubMed: 16448302]

[30]. Hughes JR, Keely JP, Niaura RS, Ossip-Klein DJ, Richmond RL, Swan GE, Measures of abstinence in clinical trials: issues and recommendations, Nicotine Tob. Res 5 (2003) 13–25. [PubMed: 12745503]

[31]. Stead LF, Bergson G, Lancaster T, Physician advice for smoking cessation (Cochrane Review), The Cochrane Library, vol. 3, Wiley Publishers, Oxford, 2008.

[32]. McAfee TA, Bush T, Deprey TM, et al., Nicotine patches and uninsured quitline callers. A randomized trial of two versus eight weeks, Am. J. Prev. Med 35 (2008) 103–110. [PubMed: 18617079]

[33]. Bush TM, McAfee T, Deprey M, et al., The impact of a free nicotine patch starter kit on quit rates in a state quit line, Nicotine Tob. Res 10 (2008) 1511–1516. [PubMed: 19023843]

[34]. Murray DM, Short BJ, Intraclass correlation among measures related to tobacco use by adolescents: estimates, correlates, and applications in intervention studies, Addict. Behav 22 (1997) 1–12. [PubMed: 9022867]

[35]. Hall SM, Humfleet GL, Munoz RF, Reus VI, Prochaska JJ, Robbins JA, Using extended cogntive behavioral treatment and medication to treat dependent smokers, Am. J. Public Health 101 (2011) 2349–2356. [PubMed: 21653904]

[36]. Hall SM, Humfleet GL, Muñoz RF, Reus VI, Robbins JA, Prochaska JJ, Extended treatment of older cigarette smokers, Addiction 104 (2009) 1043–1052. [PubMed: 19392908]

[37]. Joseph AM, Fu SS, Lindgren B, et al., Chronic disease management for tobacco dependence: a randomized, controlled trial, Arch. Intern. Med 171 (2011) 1894–1900. [PubMed: 22123795]

[38]. Altschuler J, Margolius D, Bodenheimer T, Grumbach K, Estimating a reasonable patient panel size for primary care physicians with team-based task delegation, Ann. Family Med 10 (2012) 396–400.

[39]. Chen LM, Farwell WR, Jha AK, Primary care visit duration and quality: does good care take longer? Arch. Intern. Med 169 (2009).

[40]. Geraghty EM, Franks P, Kravitz RL, Primary care visit length, quality, and satisfaction for standardized patients with depression, J. Gen. Intern. Med 22 (2007) 1641–1647. [PubMed: 17922171]

[41]. Adams ZW, McClure EA, Gray KM, Danielson CK, Treiber FA, Ruggiero KJ, Mobile devices for the remote acquisition of physiological and behavioral biomarkers in psychiatric clinical research, J. Psychiatr. Res 85 (2017) 1–14. [PubMed: 27814455]

[42]. McClure EA, Baker NL, Carpenter MJ, Treiber FA, Gray KM, Attitudes and interest in technology-based treatment and the remote monitoring of smoking among adolescents and emerging adults, J. Smok. Cessat 12 (2017) 88–98. [PubMed: 28580019]

[43]. McClure EA, Carpenter MJ, Treiber FA, Gray KM, Remotely monitoring smoking and relapse in adolescents and emerging adults, Drug Alcohol Depend 156 (2015) e145.

[44]. Meredith SE, Robinson A, Erb P, et al., A mobile-phone-based breath carbon monoxide meter to detect cigarette smoking, Nicotine Tob. Res 16 (2014) 766–773. [PubMed: 24470633]

[45]. Smith SS, McCarthy DE, Japuntich SJ, et al., Comparative effectiveness of 5 smoking cessation pharmacotherapies in primary care clinics, Arch. Intern. Med 169 (2009) 2148–2155. [PubMed: 20008701]

[46]. Cunningham JA, Kushnir V, Selby P, Tyndale RF, Zawertailo L, Leatherdale ST, Beyond quitting: Any additional impact of mailing free nicotine patches to current smokers? Nicotine Tobacco Res 20 (5) (2017) 654–655.

[47]. Welch BM, et al., Teleconsent: a novel approach to obtain informed consent for research, Contemp. Clin. Trials Commun 3 (2016) 74–79. [PubMed: 27822565]

Table 1

Clinic demographics.

Clinic	Enrollment Start	Total Patients	Race (%)		% Female	Age (M(SD))	% Smokers	Total Providers
			White	Black				
Standard care								
1	July 2014	10,622	75.0%	15.8%	57.1%	52.8(17.5)	17.3%	27
2	January 2015	1117	3.2%	95.4%	52.2%	53.1(15.7)	–	1
3	March 2015	8908	81.6%	17.1%	59.3%	66.1(15.2)	14.3%	32
4	December 2015	5972	69.5%	6.4%	58.7%	55.2(17.7)	25.4%	32
5*	November 2015	5044	94.7%	3.8%	57.4%	58.5(19.0)	17.3%	11
6†	August 2016	10,957	79.8%	17.2%	51.6%	51.8(18.2)	–	6
7	August 2016	1945	6.7%	92.3%	55.7%	50.0(15.6)	–	2
8*	September 2016	985	84.3%	15.1%	61.1%	67.9(13.9)	13.9%	3
9	May 2017	9047	36.5%	61.3%	70.1%	47.8(16.8)	26.9%	45
10	April 2017	1526	27.5%	70.1%	65.5%	46.6(16.4)	28.5%	13
11	June 2017	3400	76.1%	20.8%	62.5%	45.1(16.4)	–	35
12	October 2017	5177	50.9%	37.9%	54.1%	55.8(16.6)	–	24
NRT sampling								
13	July 2014	10,752	83.8%	9.8%	59.6%	48.1(16.4)	18.0%	27
14	August 2014	3281	89.7%	8.6%	60.0%	51.6(19.3)	16.8%	3
15	April 2015	4562	18.6%	79.1%	68.2%	44.6(16.1)	–	32
16	May 2015	3206	64.1%	31.5%	65.0%	49.1(16.4)	23.9%	63
17	August 2015	3499	52.9%	43.3%	68.0%	44.0(15.5)	–	28
18	September 2015	5926	87.4%	9.0%	58.7%	49.4(17.4)	19.5%	25
19	March 2016	4273	84.2%	13.0%	53.5%	56.2(17.9)	19.4%	24
20	June 2016	3668	91.6%	7.9%	17.3%	55.4(17.7)	15.4%	23
21	August 2016	1134	85.7%	13.3%	62.3%	64.4(14.0)	10.6%	3
22†	April 2017	3652	79.8%	17.2%	51.6%	51.8(18.2)	–	2

Note: Clinics denoted with * fell below the target enrollment pace, which resulted in enrolling two additional clinics. Clinics denoted with † were two separate sites of one clinic. Individual site data beyond patient and provider counts were not available. Demographic data are presented in aggregate across both sites. Race and smoking status data reflect prevalence among patients for whom those variables were recorded in the electronic medical record. Smoking prevalence data is only presented for clinics where at least 75% of patients had data on smoking status. Total providers reflect any health care provider responsible for patient care (not just MDs).