

Unannounced telephone pill counts for assessing varenicline adherence in a pilot clinical trial

Nia Thompson¹
Niaman Nazir¹
Lisa Sanderson Cox^{1,2}
Babalola Faseru^{1,2}
Kathy Goggin³
Jasjit S Ahluwalia⁴
Nicole L Nollen^{1,2}

¹University of Kansas School of Medicine, Department of Preventive Medicine and Public Health, Kansas City, KS, USA; ²University of Kansas Cancer Center, Kansas City, KS, USA; ³University of Missouri-Kansas City, Department of Psychology, Kansas City, MO, USA; ⁴University of Minnesota Medical School, Department of Medicine and Center for Health Equity, Minneapolis, MN, USA

Background: Despite consistent evidence linking smoking cessation pharmacotherapy adherence to better outcomes, knowledge about objective adherence measures is lacking and little attention is given to monitoring pharmacotherapy use in smoking cessation clinical trials.

Objectives: To examine unannounced telephone pill counts as a method for assessing adherence to smoking cessation pharmacotherapy.

Research design: Secondary data analysis of a randomized pilot study.

Participants: 46 moderate-to-heavy (>10 cigarettes per day) African-American smokers.

Main measures: Smokers received 1 month of varenicline (Pfizer Global Pharmaceuticals, New York, NY) in a pill box at baseline. Unannounced pill counts were completed by telephone 4 days prior to an in-person pill count conducted at Month 1. At both counts, each compartment of the pill box was opened and the number of remaining pills was recorded.

Results: Participants were a mean age of 48 years (SD = 13), predominately female (59%), low income (60% < \$1800 monthly family income), and smoked an average of 17 (SD = 7) cigarettes per day. A high degree of concordance was observed between the number of pills counted by phone and in-person ($r_s = 0.94$, $P < 0.001$). Participants with discordant counts ($n = 7$) had lower varenicline adherence (mean [SD] = 77% [18%] vs 95% [9%], $P < 0.0005$), but reported better medication adherence in the past (1.0 [0.8] vs 2.8 [1.0], $P < 0.0004$) than participants with matching phone and in-person counts ($n = 39$).

Conclusion: Unannounced telephone pill counts appear to be a reliable and practical method for measuring adherence to smoking cessation pharmacotherapy.

Keywords: medication adherence, African-Americans, smoking cessation

Introduction

Tobacco use is the most preventable cause of disease and death, accounting for 443,600 total deaths and more than 30% of all cancer deaths annually in the US.¹ Nicotine replacement therapies (NRTs) such as gum, patch, nasal spray, inhaler or lozenge, and two non-nicotine medications (bupropion (GlaxoSmithKline, Brentford, Middlesex, UK), varenicline (Pfizer Global Pharmaceuticals, New York, NY) are approved for the treatment of tobacco dependence.² While these pharmacotherapies have been shown to double or triple quit rates compared to placebo, adherence to the prescribed dose and treatment length is necessary to achieve the maximum drug effect.²⁻⁶

Despite the importance of patient adherence to smoking cessation medications, information on adherence to smoking cessation treatments is sparse. The limited evidence that is available has consistently found that better adherence to pharmacotherapy is associated with higher rates of smoking abstinence.³⁻⁹ A study by Mooney et al

Correspondence: Nia J Thompson
University of Kansas School of Medicine,
Department of Preventive Medicine
and Public Health, Mail Stop 1008,
3901 Rainbow Boulevard, Kansas City,
KA 66160, USA
Tel +1 913 220 6068
Fax +1 913 588 2780
Email nthompson3@kumc.edu

reported significantly higher week 3 and 6 abstinence rates among smokers with higher levels of adherence to bupropion,⁵ while another recently completed study found a two-fold increase in month 6 abstinence rates among participants taking varenicline on 80% of days or more compared to participants who did not meet this adherence threshold (52% vs 25%).⁷ As well, Shiffman et al found that the odds of abstinence at 6 weeks was three times greater among participants adherent to nicotine patch compared to those who were non-adherent (53.2% vs 21.5%, respectively).⁶

Lack of attention to pharmacotherapy adherence in smoking cessation studies may be due, in part, to lack of consensus on the best objective adherence measures.¹⁰ Methods of assessing adherence are divided into two categories: direct and indirect assessment. Direct assessment includes detection of the drug in biologic fluids, direct observation, and detection of biological markers. The common advantage of direct methods assessment is greater certainty that the drug has been consumed because there is no reliance on the truthfulness of the patient.² Direct methods are not utilized as often as indirect methods because of cost feasibility. Detection of metabolites or drugs in biologic fluids such as blood or urine is a quantitative measure. This method of measurement is very accurate as it can confirm recent use of medication by detecting the levels in bodily fluids.¹¹ Disadvantages include a limited time frame to use this measure, kinetic variations among individuals, high cost, and inconvenience to the patient.^{12,13} Direct observation assessment includes visually observing the patient consuming the medication. Advantages of this type of assessment include visual confirmation of medication consumption. However, direct observation is impractical for daily use and patients can hide pills in their mouths and later throw them away.^{12,13}

Indirect methods of assessment, such as questionnaires, diaries, clinical response, prescription refills, electronic medication monitors, and pill counts, rely upon self-assessment by the patient, but the uncertainty about whether a patient has, in fact, consumed the medication is a disadvantage of indirect assessment.¹¹⁻¹³ Questionnaires and diaries are the most basic level of self-reporting. They are advantageous because they help with recall, are effective in a clinical setting, and are efficient in understanding a patient's medication regimen. These methods are subject to recall bias and misinterpretation of questions may lead to over estimation of patient adherence.¹² In general the rate of medication refill is an accurate method to evaluate medication adherence.¹³ The rates of prescription refills are a rapid and easy way to measure medication adherence. In a Health Maintenance Organization

or Universal Health Care system this is an effective way for physicians and health care providers to gain a scope of adherence. The major disadvantage to this methodology is that obtaining the medication is not equivalent to consuming or utilizing the medication.¹³ Electronic monitoring of medication adherence is achieved through the use of the Medication Event Monitoring System (MEMS). MEMS has the ability to record and stamp the time of opening medication bottles, dispensing drops, or activation of canister.¹³ This type of device provides accuracy and precision on the exact timing of medication and regimens.^{12,13} While MEMS is a valid and reliable measure, there are many disadvantages to this method of analysis.¹¹⁻¹³ First, the removal of the medication cap does not confirm that the patient actually took the medication. In addition, the poor health of smokers indicates that many of these individuals take a variety of medications for smoking attributable conditions. Therefore many smokers do not use individual medication bottles due to the number of medications they are prescribed; it is easier to use pill boxes for organization.¹² These logistics suggest a major barrier in the use of MEMS for smokers and tobacco cessation medication adherence. In addition, MEMS technology is fairly expensive and unfeasible outside of clinical trials.¹⁴ Due to disadvantages and inconsistencies in other measures, the pill count is a commonly used indirect adherence measure.¹⁵

Pill counts are an established, objective method for assessing medication adherence.^{13,16} However, they are limited by a number of factors. Notably, pill counts are typically conducted in-person and can be a burden to participants by requiring them to come to a clinic and remember to bring their medications.^{13,17} In-person pill counts may also be inaccurate if participants remove medications from their container in anticipation of a pill count. Unannounced pill counts completed by telephone may be a viable and more practical alternative. Unannounced telephone pill counts have been examined as an alternative to in-person pill counts in other health domains,^{16,18-20} but to our knowledge, have not been examined as a tool for assessing adherence to smoking cessation pharmacotherapy. Given the potential for pharmacotherapy adherence to improve tobacco treatment outcomes but the lack of objective, practical assessment tools, this study examined unannounced telephone pill counts for assessing adherence to smoking cessation pharmacotherapy by comparing telephone counts to in-person counts completed approximately 4 days later. Demographic, psychosocial, and medication/treatment-related differences were also examined between participants who had perfectly concordant vs discrepant telephone and in-person pill counts.

Methods

Parent study

The parent pilot trial, described in detail elsewhere, examined a behavioral intervention to encourage medication compliance among African-American smokers taking varenicline.⁹ Participants were recruited through clinic-based efforts, including lobby recruitment and the use of posters and flyers, as well as through a tracking database of participants ineligible for another study who had given their consent to be contacted for future studies. Of the 308 people screened, 192 were medically ineligible, 116 were eligible and invited to participate, and 44 did not keep their baseline appointment, leaving a final sample of 72 participants. Medically eligible smokers were randomly assigned to Adherence Support (AS; $n = 36$) or Standard Care (SC; $n = 36$). Participants randomized to Standard Care received 3 months of varenicline, standard quit smoking educational materials, and counseling focused on setting a quit date. Participants randomized to Adherence Support received everything that Standard Care participants received plus five additional counseling sessions to encourage adherence to varenicline. Counseling sessions were conducted in-person on Day 0/Baseline (AS and SC), Day 12 (AS), Month 1 (AS), and Month 2 (AS), and by phone on Day 8 (AS) and Day 20 (AS).

Sub-sample

All 72 participants in the parent study were contacted for telephone pill counts, however, 13 were lost to follow-up at Month 1, eleven completed one pill count (telephone or in-person) but not both, and two pocketed too many doses of their medications to be reliably counted, leaving a final sample of 46 participants (22 SC, 24 AS) with complete Month 1 unannounced telephone and in-person pill count data. These 46 comprise the sub-sample for the current study.

Participants and screening

Inclusion criteria included being African-American, ≥ 18 years of age, smoking >10 cigarettes per day, being interested in quitting, willing to take varenicline, and having a functioning telephone number. Participants were excluded if they were planning to move from the area within 3 months or had contraindications to the use of varenicline, including: a cardiovascular event in the month prior to enrollment; renal impairment; taking insulin for diabetes but unwilling to closely monitor blood sugar; history of clinically significant allergic reactions to varenicline; a major depressive disorder in the past year requiring treatment; history of alcohol or drug dependency in the

past year; history of psychosis, panic disorder, bipolar disorder or any eating disorders; or current breast-feeding, pregnancy or plans to get pregnant in the next 3 months.²¹ Participants were enrolled between March and August 2009. Written informed consent was obtained from all participants. All study procedures were approved and monitored by the University of Kansas Medical Center's human subjects committee.

Medication dispensing

Participants received a 1-month supply of varenicline, or 57 pills, dosed according to standard guidelines in a 30-day pill box at baseline. Participants were scheduled to return to the clinic at Month 1 for a medication refill.

Pill counts

Pill counts were completed by trained research staff following a standardized protocol adapted from previous studies whereby the number of pills remaining in each compartment of the pill box (ie, 0, 1, or 2 pills) was opened and recorded.^{18–20} Participants were told that they would receive periodic checks to assess their experience with the medication; however, they were unaware that a pill count would be completed at either the Month 1 refill visit or by phone a few days prior to this visit.

Unannounced telephone pill count

Unannounced telephone assessments occurred 3–4 days prior to the Month 1 visit. Research staff phoned participants, confirmed that it was a good time for them to talk, and asked them to retrieve their pill box. Following a standardized script, participants were told that the assessments were being done to better understand what people in the study were doing with their pills. They were told not to worry about telling the research staff if they missed or had stopped taking their medication because the purpose was to understand the good and bad aspects of taking the medication so that we could better help participants in the future. Research staff then asked participants to open each compartment of their pill box, one-by-one, and to report the number of pills remaining in each compartment.

In-person pill counts

In-person pill counts were completed by research staff at the Month 1, 2, and 3 medication refill visits. In-person counts followed the exact same protocol and script as the telephone counts, the only difference being that research staff, not the participant, opened and recorded the number of pills observed in each compartment.

Outcome variables

Concordance of pills counted

The number of pills remaining in each compartment of the pill box (ie, untaken/missed doses) was recorded onto data sheets and summed to provide the total number of pills counted. Separate data sheets were completed for the unannounced and in-person pill count assessment to limit the potential for bias. For ease of interpretation, the days between completion of the unannounced pill count and the in-person assessment were excluded so that the sum of pills counted by telephone and in-person were for the exact same time frame.

Other variables of interest

Baseline demographic, psychosocial, and medication/treatment-related variables were included to examine if participants with discordant phone and in-person pill counts differed from participants with perfectly concordant counts. Variables were selected based on factors known to be associated with poor adherence in the literature.^{13,22}

Demographic characteristics

Demographic information included age, gender, education, marital status, monthly family income, cigarettes smoked per day, and type of cigarette smoked (menthol, non-menthol).²³ The three-item Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) was used to assess problem drinking, with scores of three or greater indicating possible problems with alcohol.^{24,25} Use of marijuana or other drugs was assessed using a single item, "During the past 7 days, have you smoked marijuana or used other drugs."

Psychosocial characteristics

The ten-item Center for Epidemiological Studies Depression Scale (CES-D) was used to measure psychological distress, with scores of ten or higher indicating possible clinical depression.²⁶ A single item assessed motivation and confidence to quit smoking on a ten-point continuum ranging from 'Not at all important/confident' to 'Extremely important/confident.' This item has been used to assess motivation and confidence to quit smoking in other studies.²⁷⁻³⁰ A five-item motivation to adhere scale was used to assess participant's motivation to take varenicline. This measure is grounded in motivational interviewing principles and has been found to be a reliable and valid measure of motivation to adhere to HIV medications.^{31,32} Confidence to take varenicline in the face of common challenges – eg, changing eating habits, making them feel sick – was assessed using an adapted version of the ten-item HIV treatment adherence self-efficacy scale.³³

The six-item God Locus of Health Control (GLHC) measure was used to assess participant's perception of God's control over whether they quit smoking.³⁴

Medication/treatment-related characteristics

Adherence was computed from the Month 1 in-person pill count by dividing the number of pills taken (pills prescribed minus pills counted) by the number of pills prescribed times 100. For example, participants were prescribed 57 pills during month 1. If three pills were counted, adherence was calculated as $57 - 3 \text{ [pills taken]} / 57 \times 100$. Participants were asked about ten symptoms associated with quitting smoking and/or smoking cessation pharmacotherapy (eg, fatigue, trouble sleeping, irritability), including the severity of each reported symptom. A similar medication symptoms checklist has been used in published clinical trials to examine side effects of varenicline.^{21,35-43} Past medication taking behaviors were assessed using the Medication Adherence Questionnaire.^{44,45} Treatment group assignment (Adherence Support vs Standard Care) was compared between participants with concordant and discrepant pill counts.

Statistical analyses

Continuous variables were described using mean and standard deviation. Similarly, categorical variables were described using frequency and percentage. We primarily performed analyses to assess the concordance between the unannounced telephone and in-person based pill counts. We tested agreement using Spearman's correlation. Using the non-parametric Wilcoxon for continuous variables and the Fischer's exact test for categorical variables, we compared participants who had perfectly concordant unannounced telephone and in-person pill counts with participants who had discrepant pill counts on demographic and psychosocial characteristics. Given the small sample size and the number of comparisons, Bonferroni corrections were applied to these comparisons such that only those variables significant at $P < 0.003$ were considered statistically significant. All analyses were performed using SAS (©2002–2008 by SAS Institute Inc, Cary, NC).

Results

Participants

No statistically significant differences were found on any of the demographic, psychosocial, or medication/treatment-related factors between our sub-sample of 46 and the 26 participants in the parent study with incomplete data who were excluded from the current analyses. Participants were all African-American, 27 women and 19 men, with a mean

age of 48.1 (SD = 12.6) years. The majority (82.6%) had a high school education or more but were predominately low income (59.5% had a family income of <\$1,800/month). Participants smoked menthol cigarettes (80.4%), averaged 17.1 (SD = 6.7) cigarettes per day and were highly motivated to quit smoking (9.9 [SD = 0.5] out of a possible 10).

Concordance of pills counted

Unannounced telephone pill counts were completed an average of 4.2 (SD = 3.9) days before the in-person pill count. The correlation between the phone and in-person pill counts was $r_s = 0.94$ ($P < 0.0001$), with an average of 3.6 (7.1) pills being counted by telephone and 3.9 (7.1) pills being counted in-person. Contacting 46 participants for the unannounced telephone pill count required a total of 85 call attempts, with 20 (43.4%) participants contacted on their first attempt, 13 (28.3%) contacted on their second attempt, and 13 (28.3%) requiring three or more phone attempts to reach them. A summary of costs for the telephone and in-person pill counts is shown in Table 1. The average cost per telephone pill count was \$2.18, while the average cost per in-person pill count was \$7.24.

Analysis of discrepant counts

Of the 46 participants, 39 participants (85%) had Month 1 unannounced phone and in-person pill counts that were exactly the same – ie, concordant – and seven (15%) had unannounced phone and in person pill counts that were discordant. Analysis of the seven discordant counts showed that a mean of 4.0 (SD = 3.2) fewer pills were counted over the phone compared to in-person (ie, missed pills were underreported over the phone). Comparisons between participants with discordant pill counts ($n = 7$), and those who had precisely the same unannounced telephone and in-person pill counts ($n = 39$) are shown in Table 2A and B. Participants with discrepant pill counts had lower medication adherence rates at Month 1 (77% [18%] vs 95% [9%], $P < 0.0005$); however, they reported better adherence to medications in the past (1.0 [0.8] vs 2.8 [1.0], $P < 0.0004$) compared to participants with matching phone and in-person pill counts.

Discussion

This study obtained high levels of concordance for pills counted and medication adherence rates between unannounced pill counts by telephone and those conducted in-person. These findings are consistent with other health studies that have found concordance rates of 0.981–0.997 between unannounced telephone and in-person pill counts.^{19,20} Consistent relationships have been found between pharmacotherapy use

Table 1 Summary of costs for the telephone vs in-person pill counts

Cost variables	Telephone pill count	In-person pill count
Salary with fringe benefits	\$13.05 per hour	\$13.05 per hour
Time spent reaching participants for pill count	2 minutes	–
Time spent counting pills	8 minutes	8 minutes
Phone line	\$0.03 per hour	–
Average participant mileage to clinic	–	10 miles
Mileage reimbursement	–	\$0.55/mile
Total costs	\$2.18 per pill count	\$7.24 per pill count

and higher rates of smoking abstinence,^{3–6,46} yet little attention is given to monitoring pharmacotherapy use in smoking cessation clinical trials. Findings from this study suggest that unannounced telephone pill counts may be a viable and practical alternative for objectively measuring pharmacotherapy adherence in smoking cessation clinical trials.

Unannounced telephone pill counts may be more feasible to implement than in-person counts and have a number of advantages over other approaches.^{13,19} Unannounced telephone pill counts minimize many challenges associated with office-based pill counts (eg, dumping pills in anticipation of a pill count, forgetting medication for the office visit) and reduce participant burden (eg, time and travel), which allows for more regular monitoring of medication taking. Nearly half of the participants in this study were contacted on their first attempt, with the majority being contacted on the first or second attempt. Telephone pill counts also cost less than in-person counts. The cost per telephone pill count in this study was \$2.18 compared to \$7.24 for the in-person counts. These figures are similar to a study conducted by Kalichman et al which found that phone-based pill counts cost \$7.65, on average, compared to \$19.61 for in-person counts, and suggests that telephone pill counts are more cost effective to implement than in-person counts.²⁰

Pill boxes were used in this study to simplify and improve the accuracy of the pill count protocol – ie, participants opened each pill box compartment and reported the number of pills remaining; they did not have to remove varenicline from pill bottles, sort, and count their medication using pharmacy trays, an approach that may be prone to lost pills and counting errors. Although other studies have shown that pill boxes may lead to increased error and misreporting,^{19,20} pill boxes appeared to be useful in this study. The mean rate of adherence to varenicline was 92%. This is consistent with research showing that adherence to medications is higher among participants who use a pill box compared to those who do not.⁴⁷ We did not

Table 2A Baseline continuous demographic, psychosocial, and medication/treatment related characteristics of participants with discordant and concordant pill counts (N = 46)^a

Characteristic	Discordant pill counts	Concordant pill counts	P
	(N = 7)	(N = 39)	
Demographic			
Age	48.7 (13.4)	47.9 (12.7)	ns
Psychosocial			
Alcohol use (AUDIT-C; 0–12), ^b mean, (SD)	1.9 (1.6)	2.8 (2.7)	ns
Depression (CES-D-10; 0–30) ^c mean, (SD)	6.9 (6.7)	7.3 (5.4)	ns
God's control over quitting (GLHC; 0–36), mean, (SD)	26.7 (10.8)	18.7 (9.3)	ns
Motivation to take medication (0–50), mean, (SD)	43.7 (10.4)	49.3 (1.3)	ns
Confidence to take medication (0–100), mean, (SD)	92.3 (12.1)	91.1 (9.5)	ns
Motivation to quit smoking (0–10), mean, (SD)	10.0 (0.0)	9.8 (0.1)	ns
Confidence to quit smoking (0–10), mean, (SD)	9.0 (1.9)	8.5 (1.8)	ns
Medication/treatment-related			
Number of moderate to severe side effects, mean, (SD)	0.9 (0.9)	0.5 (0.9)	ns
Prior medication adherence (MAQ; 0–4), ^e mean, (SD)	1.0 (0.8)	2.8 (1.0)	0.0004
Month 1% adherence (per in-person pill counts), mean, (SD)	77 (0.18)	95 (0.09)	0.0005

Notes: ^aAll measures were taken at baseline, unless otherwise noted; ^bAlcohol Use Disorders Identification Test-Consumption; ^cCenter for Epidemiological Studies Depression Scale; ^dGod Locus of Health Control; ^eMedication Adherence Questionnaire (higher scores indicate non-compliance).

Abbreviations: SD, standard deviation; CES-D, Center for Epidemiological Studies Depression Scale; GLHC, God Locus of Health Control; MAQ, Medication Adherence Questionnaire.

have a no-pill box comparison group in this study, and cannot conclude that the use of pill boxes led to increased adherence. However, pill boxes are a method of organization; participants can open a compartment to easily determine whether they have taken the medication on a given day compared to a pill bottle where the determination of whether medication has been taken is more difficult. Given the use of pill boxes as a common adherence aid and previous research that has found that pill boxes increase medication adherence by as much as 5% compared to a no-pill box condition,⁴⁷ we speculate that pill boxes used in conjunction with unannounced telephone monitoring could improve medication adherence and, in turn, increase rates of smoking abstinence. Pill boxes may also be preferred over other methods of medication monitoring. In a community-based sample of predominately low-income African-American

women with hypertension, one-third preferred a pill box over a Medication Event Monitoring System (MEMS), an electronic bottle cap that records the exact date and times that bottles are opened,⁴⁸ suggesting that pill boxes may be a better tool for monitoring adherence in some populations.

The study has limitations. First, this is a pilot study with a small sample size comprised of mostly African-American women recruited from a single community health center; therefore results may not generalize to a more diverse sample. Second, due to the small sample size and the relatively low number of participants with discrepant counts, comparisons between participants with concordant and discrepant pill counts were limited in the power to detect statistically significant differences and the differences found should be interpreted with caution. Finally, it is possible that participants

Table 2B Categorical demographic, psychosocial, and medication/treatment related characteristics of participants with discordant and concordant pill counts (N = 46)

Characteristic	Discordant pill counts	Concordant pill counts	P
	(N = 7)	(N = 39)	
Demographic			
Female, n (%)	6 (85.7%)	21 (53.9%)	ns
Married or living with partner, n (%)	3 (42.9%)	15 (38.5%)	ns
Monthly family income <\$1,800, n (%)	5 (71.4%)	20 (57.1%)	ns
<High school education, n (%)	2 (28.6%)	6 (15.4%)	ns
Menthol cigarettes, n (%)	6 (85.7%)	31 (81.6%)	ns
Use of marijuana or other drugs, n (%)	1 (14.3%)	4 (10.3%)	ns
Psychosocial			
Possible clinical depression, n (%)	2 (28.6%)	11 (28.2%)	ns
Treatment-related			
Treatment group, adherence support, n (%)	6 (85.7%)	18 (46.2%)	ns

anticipated having their medications counted during the Month 1 refill visit and removed pills after the unannounced telephone pill count. We safeguarded against this possibility by blinding participants to both pill counts. In addition, we achieved concordance rates for pills counted that are similar to those achieved in studies where in-person counts were completed immediately following telephone counts.^{19,20}

Further research is needed among a larger and more diverse sample to confirm and improve the generalizability of the findings. Research is also needed to compare the utility of unannounced telephone pill counts for smoking cessation pharmacotherapy with other objective methods of medication monitoring – eg, MEMS, immediate in-person unannounced pill counts. Studies in other health domains have found a high degree of concordance between unannounced telephone pill counts and electronic (MEMS) monitoring,^{16,18} but this should be confirmed with smoking cessation pharmacotherapy. Each method has its respective advantages and disadvantages. Telephone pill counts may be preferred among some populations⁴⁸ and may lend themselves best to non-nicotine therapies – ie, varenicline, bupropion. Methods for monitoring use of NRTs – ie, nicotine gum, patch, nasal spray, inhaler, and lozenge – warrant further attention.

In conclusion, better strategies are needed to monitor medication adherence in smoking cessation clinical trials. Unannounced telephone pill counts may represent one such approach. Telephone pill counts are feasible and may reduce burden and costs compared to in-person counts.

Acknowledgments

Contributors: None to report.

Funder: This study was supported by a grant from the (University of Kansas Cancer Center, Kansas City, KS) and a contract from (Pfizer Global Pharmaceuticals, New York, NY) (GA3051YA). Pfizer provided study medication, but played no role in the study design, conduct of the study, or interpretation and analysis of the data.

Prior presentations: This paper was presented as a poster at the 2011 (February) Annual Meeting of the Society of Research on Nicotine and Tobacco, Toronto, ON.

Disclosure

Nia Thompson: No conflicts of interest.

Nicole L Nollen: This study was supported by a contract from Pfizer Global Pharmaceuticals to Dr Nollen (GA3051YA). Pfizer provided study medication, but played no role in the study design, conduct of the study, or interpretation and analysis of the data.

Niaman Nazir: No conflicts of interest.

Lisa Sanderson Cox: No conflicts of interest.

Babalola Faseru: No conflicts of interest.

Kathy Goggin: No conflicts of interest.

jasjit S Ahluwalia: Dr Ahluwalia serves as a paid consultant to Pfizer Inc, which markets varenicline.

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