


Accuracy of self-reported smoking abstinence in clinical trials of hospital-initiated smoking interventions

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ABSTRACT

Aims To estimate the prevalence and predictors of failed biochemical verification of self-reported abstinence among participants enrolled in trials of hospital-initiated smoking cessation interventions. **Design** Comparison of characteristics between participants who verified and those who failed to verify self-reported abstinence. **Settings** Multi-site randomized clinical trials conducted between 2010 and 2014 in hospitals throughout the United States. **Participants** Recently hospitalized smokers who reported tobacco abstinence 6 months post-randomization and provided a saliva sample for verification purposes ($n = 822$). **Measurements** Outcomes were salivary cotinine-verified smoking abstinence at 10 and 15 ng/ml cut-points. Predictors and correlates included participant demographics and tobacco use; hospital diagnoses and treatment; and study characteristics collected via surveys and electronic medical records. **Findings** Usable samples were returned by 69.8% of the 1178 eligible trial participants who reported 7-day point prevalence abstinence. The proportion of participants verified as quit was 57.8% [95% confidence interval (CI) = 54.4, 61.2; 10 ng/ml cut-off] or 60.6% (95% CI = 57.2, 63.9; 15 ng/ml). Factors associated independently with verification at 10 ng/ml were education beyond high school education [odds ratio (OR) = 1.51; 95% CI = 1.07, 2.11], continuous abstinence since hospitalization (OR = 2.82; 95% CI = 2.02, 3.94), mailed versus in-person sample (OR = 3.20; 95% CI = 1.96, 5.21) and race. African American participants were less likely to verify abstinence than white participants (OR = 0.64; 95% CI = 0.44, 0.93). Findings were similar for verification at 15 ng/ml. Verification rates did not differ by treatment group. **Conclusions** In the United States, high rates (40%) of recently hospitalized smokers enrolled in smoking cessation trials fail biochemical verification of their self-reported abstinence.

Keywords Biochemical verification, hospital patients, saliva cotinine, self-report, smoking cessation, trials.

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INTRODUCTION

Assessing smoking abstinence is a challenge for smoking cessation trials [1,2]. Self-reported abstinence is a simple and convenient method, but participants do not always report their smoking status accurately [3]. As a result, biochemical measures of tobacco use are considered the gold standard for outcomes in clinical trials. Biochemical measures may be more accurate in assessing tobacco use,

but this advantage must be weighed against their costs and limitations.

Biochemical verification may not be necessary for determining the prevalence of tobacco use in the general population. Population-based epidemiological studies suggest that rates of failed biochemical verification of non-smoking status are low, with country estimates ranging from approximately 1% in the United States to 4% in Poland [4–6]. While these general population studies suggest that

misreporting is low, specific subgroups may be more likely to fail verification. Studies have found higher rates of misreporting among individuals in clinical situations where tobacco use is especially stigmatized, such as pregnant women [7], patients with cardiac disease [8] and patients with respiratory illness [9].

Similarly, verification may not always be necessary in determining the outcomes of smoking cessation trials in which investigators are trying to determine the relative effectiveness of different treatments. The Society for Research on Nicotine and Tobacco (SRNT) Subcommittee on Biochemical Verification conducted a meta-analysis and found that, using a complete-case approach, only 12.9% of outcome comparisons showed that treatment outcome was affected by biochemical verification [10]. Findings were similar for intent-to-treat analyses. Where discrepancies occurred, significant effects were typically found using self-report, but not found using biochemical verification. There were two exceptions where biochemical verification yielded a significant treatment effect when self-report did not—these two studies occurred among pregnant smokers. These findings show that differences between self-reported outcomes and biochemically verified outcomes can cause investigators to either falsely reject or fail to reject the null hypothesis.

Several study characteristics may enhance the need for biochemical verification. To help researchers determine when verification might be necessary, the SRNT Subcommittee identified three overarching factors that should be considered: (1) demand characteristics, (2) type of population and (3) type of study [10]. Varying levels of contact with study staff across treatment arms may create a demand bias that could cause smokers in intervention arms to misreport abstinence at a higher rate. The type of population can be categorized as the general population or specific groups such as medical patients, with special groups often experiencing heightened perceived pressures to quit smoking that increase the likelihood of misreporting [8]. Due to one or more of these factors, biochemical verification of smoking abstinence may be needed in randomized trials testing the effectiveness of cessation interventions.

While several studies have investigated the accuracy of self-reported smoking status compared to biomarkers for tobacco use [3,11], there is little empirical evidence regarding population and study characteristics associated with discrepancies between self-report and validated abstinence in clinical trials. Factors such as education, age, race/ethnicity, diagnosis, number of smokers in the household and even inadvertent exposure to carbon monoxide have been associated with the failure of self-report to match biochemical measures [4,8,12]. These studies indicate that demographic and health status characteristics are important in understanding verification failures. However, important gaps remain in understanding the degree

to which intervention intensity, health status and other patient characteristics contribute to failed verification, especially in the context of clinical trials.

This study used data from a set of smoking cessation intervention trials with hospitalized smokers to address the gaps in the discourse on verification of smoking status. These National Institutes of Health (NIH)-funded randomized controlled trials comprise the Consortium of Hospitals Advancing Research on Tobacco (CHART). CHART was formed with the goal of conducting translational research on effective smoking cessation interventions initiated during in-patient hospital stays and continuing post-discharge [13].

The aims of this study were to: (1) estimate the prevalence of failed verification of self-reported abstinence in clinical trials; (2) estimate the extent to which participant demographics, study characteristics (e.g. sample collection methods) and population factors (e.g. diagnoses provided during hospitalization) are associated with verification of smoking abstinence; and (3) estimate rates of self-reported relapse, other tobacco/nicotine exposures and verification based on surveys included in sample collection kits.

METHODS

Design

The design is a cross-sectional descriptive study comparing the characteristics of participants who verified and those who failed to verify self-reported abstinence. Five of the eight CHART trials participated in this substudy. CHART was funded jointly by the National Heart, Lung and Blood Institute, National Cancer Institute, National Institute on Drug Abuse and NIH Office of Behavioral and Social Science Research. CHART researchers collaboratively created a set of core baseline measures and follow-up assessments. CHART trials used similar eligibility criteria. Each trial compared a post-discharge intervention to usual care. The interventions included a web-based program [14], interactive voice-response (IVR) support [15], staff-provided counseling [16], quitline counseling [17,18] and provision of nicotine patches [18].

Participants were enrolled during their hospital stay and provided informed consent and baseline data before being randomized to treatment arm. Trials conducted in Birmingham, AL [14], Boston, MA [15], Kansas City, KS [17], New York, NY [16] and San Diego and Davis, CA [18] used salivary cotinine to verify self-reported smoking abstinence biochemically at 6 months after randomization using a shared protocol. This shared protocol was designed to yield high return rates and collect comparable data for pooled analyses. Institutional Review Boards at each study site approved all study procedures and permitted de-identified data to be shared across CHART.

Participants

Participants in the CHART studies who self-reported 7-day point prevalence tobacco abstinence at 6-month post-randomization follow-up were asked to provide a saliva sample. Participants were ineligible for cotinine verification if they self-reported current use of other forms of tobacco, electronic cigarettes (e-cigarettes) or nicotine replacement therapy (NRT). One trial conducted its own study on the effects of high (\$100) versus low (\$20) reimbursement for returning saliva kits [18]; participants reporting 7-day abstinence at 6 months were randomized to one of the two reimbursement conditions. Only participants receiving high reimbursement (consistent with the range of reimbursement of other CHART studies) were included in the current analyses. A second trial collected saliva samples only during a 14-month period of their trial; no samples were collected for the remainder of the study [16].

Procedures

Participants completed the 6-month follow-up survey via telephone, reported their smoking status and were screened for eligibility for cotinine verification. Participants who self-reported 7-day abstinence and were otherwise eligible were either mailed kits containing self-addressed, pre-paid return envelopes with instructions to provide a saliva sample or asked to provide a saliva sample in person. Two of the five studies collected samples via mail only; three studies collected samples via mail and in person. Two studies invited individuals who lived within the local area to attend the clinic, meet at a public place or schedule a home visit to provide a saliva sample. The third study that collected in-person samples did so among a small number of participants who were re-hospitalized during the sample collection window.

Reimbursement for returning a sample ranged from \$50 (one study) to \$100 (four studies). One of the studies reimbursed participants \$100 for in-person samples and \$75 for mailed samples. Participants were generally reimbursed by check or gift card. To ensure high return rates, the protocol was to make up to five attempts via phone and/or mailed reminders to obtain saliva samples. Only samples returned within 30 days of the 6-month survey date were analyzed.

Saliva samples were collected via self-administered oral swabs which were then enclosed in protective tubes for storage and shipping. Samples were stored in a standard freezer and mailed in batches for analysis at Salimetrics. Salivary cotinine was analyzed by enzyme immunoassay (EIA), which has a limit of quantification of 0.15 ng/ml and produces results comparable to gas chromatography/mass spectroscopy [19,20] and liquid

chromatography/mass spectroscopy [21], but may yield more false negatives [21].

Three of the five projects included a brief survey in the mailed kit that asked about past 7-day tobacco or nicotine product use and second-hand smoke exposure in the 24 hours before sample collection. A fourth project included a survey in the mailed kit that assessed past 7-day smoking among the last 40 participants who were eligible for cotinine verification. These surveys were returned to the researchers along with the saliva sample.

Measures

Predictors

Baseline variables included age, gender, race, ethnicity and education. At 6-month follow-up, participants reported whether they lived with another smoker, whether they had smoked at all since hospital discharge and whether they had smoked in the previous 7 days (point prevalence abstinence).

Information for the hospital stay during which participants were enrolled was extracted from each participant's electronic medical record: primary and secondary discharge diagnoses, whether admission was through the emergency department and insurance status. Diagnoses were categorized using ICD-9 codes for neoplasms, respiratory diseases, cardiovascular diseases and mental health disorders. Primary discharge diagnosis codes for neoplasms, respiratory diseases and cardiovascular diseases were combined to indicate smoking-related diseases. Detailed descriptions of the core measures are provided elsewhere [13].

Outcomes

Two cut-points were used for cotinine verification of self-report: 10 ng/ml, a widely adopted threshold for active smoking in recent smoking cessation clinical trials [22–24] and the higher cut-point of 15 ng/ml recommended by the SRNT Subcommittee on Biochemical Verification [10]. Although lower cut-points have been recommended based on population data [25], we retained higher cut-points because ex-smokers may be exposed to more environmental tobacco smoke than non-smokers in the general population [26]. The two cut-points were used to create dichotomous variables for verification (1 = cotinine verified, 0 = failed verification).

Statistical analyses

Descriptive statistics were computed for participant characteristics. Logistic regressions were used to compare participant characteristics between those who were eligible and returned a usable sample and participants who were eligible who did not return a usable sample. We calculated

the proportion of participants whose self-reported smoking abstinence was verified using the 10 and 15 ng/ml cut-points.

In order to identify predictors of verification of smoking abstinence in the study sample, we used logistic regressions to determine differences between participants who were verified as abstinent versus failed verification. Comparisons were made on: demographic characteristics, Medicaid insurance status, discharge diagnoses, whether the participant smoked since hospital discharge and study-related characteristics. We tested multivariable logistic regressions to examine the associations of the demographic, insurance, smoking-status and study-related characteristics on verification of abstinence using 10 and 15 ng/ml cut-points. In a preliminary analysis, we included study site as a random effect in logistic regression models to allow for possible heterogeneity of effect across study sites. These effects were negligible and non-significant, and hence were dropped as a model component.

Using data from the subset of participants who completed the survey mailed with the saliva kit, we calculated the proportions of participants who reported (1) smoking in the past 7 days, (2) other tobacco use (e-cigarettes were included in this category), (3) nicotine replacement therapy use and (4) past 24-hour second-hand smoke exposure. As a subanalysis, we estimated verification rates of participants who reported past 24-hour second-hand

smoke exposure and rates of those reporting none. All analyses were conducted using SPSS version 23.0.

RESULTS

Figure 1 presents the flow diagram for participants in this study. In the five participating trials, 4206 participants completed the 6-month survey. Of these, 1708 reported 7-day abstinence but 530 were ineligible for the study. The sample size was reduced further by 36 refusals, 219 samples not returned, 15 with insufficient amounts of saliva and 86 samples returned more than 30 days after completion of the 6-month survey. This resulted in a final sample of 822, 69.8% of 1178 participants who were eligible for cotinine verification. Samples were collected via mail ($n = 670$) and in person ($n = 152$). Mailed samples were received an average of 14.5 days [standard deviation (SD) = 6.8] after the 6-month survey and the mean for in-person collection was 8.7 days (SD = 8.8).

Descriptive statistics for eligible participants who returned usable samples versus those who did not are presented in Table 1. The majority were white (56.1%) and 32.6% were African American. American Indian (1.7%), Asian/Pacific Islander (1.2%) and multi-racial (3.5%) were combined for analytical purposes into 'Other race' (4.9%). There were few differences between eligible participants who returned usable samples ($n = 822$) versus those who

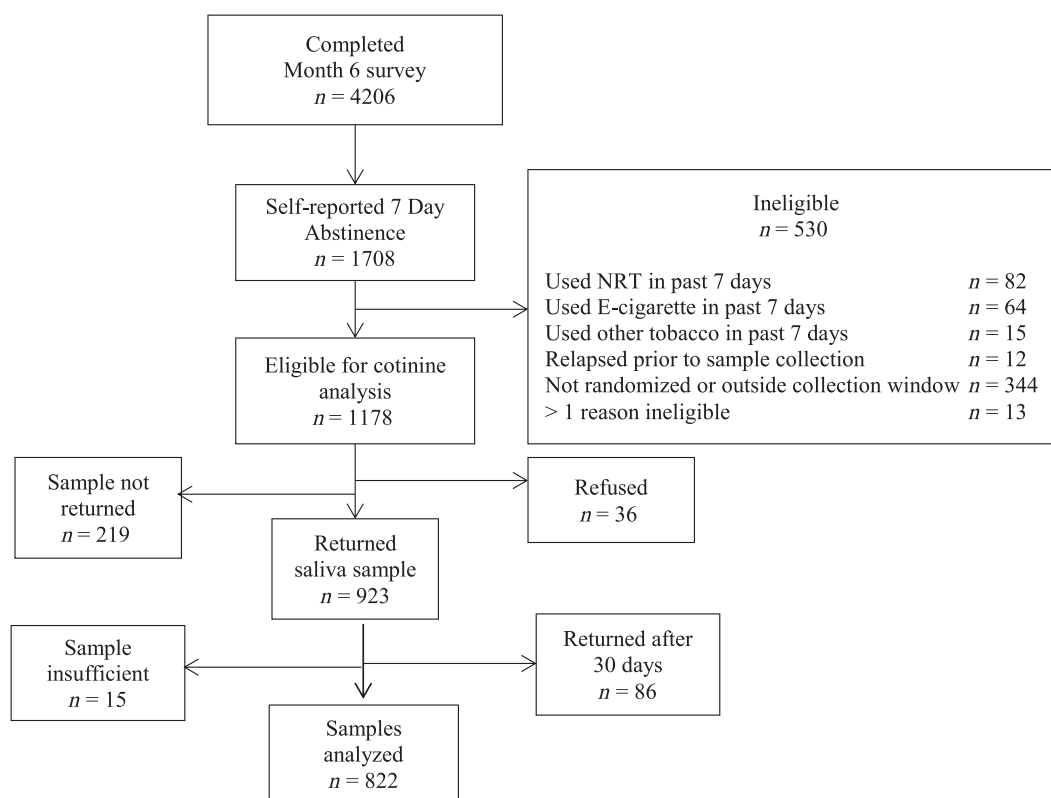


Figure 1 Flow diagram for cotinine verification study

Table 1 Baseline characteristics of participants eligible for biochemical verification by sample status.

	Returned usable sample (n = 822)	Did not return usable sample (n = 356)	
	% or mean (SD)		P-value
Age (years)			0.595
18–44, %	35.7	33.4	
45–64, %	52.7	55.9	
≥ 65, %	11.6	10.7	
Male, %	56.4	54.4	0.537
Education			
> high school, %	44.0	47.2	0.320
Race			0.045
White, %	56.1	63.2	
African American/black, %	32.6	25.6	
Other, %	11.3	11.2	
Ethnicity			
Latino, %	11.9	14.0	0.313
Primary discharge diagnosis			
Cardiovascular diseases, %	15.7	9.6	0.005
Respiratory diseases, %	4.9	1.1	0.002
Neoplasms, %	0.9	1.1	0.656
Mental health disorders, %	1.5	0.8	0.386
Secondary diagnosis			
Mental health disorder, %	45.6	31.2	<0.001
Cigarettes per day, mean (SD)	13.54 (10.82)	12.76 (8.83)	0.229
Daily smoking (≥ 25 days/month), %	74.1	77.2	0.658
Past 30-day other tobacco use, %	7.4	6.9	0.773
Treatment intervention group, %	53.4	57.3	0.218

SD = standard deviation.

did not ($n = 356$); higher proportions of African Americans and participants with primary discharge diagnoses of cardiovascular or respiratory diseases returned usable samples

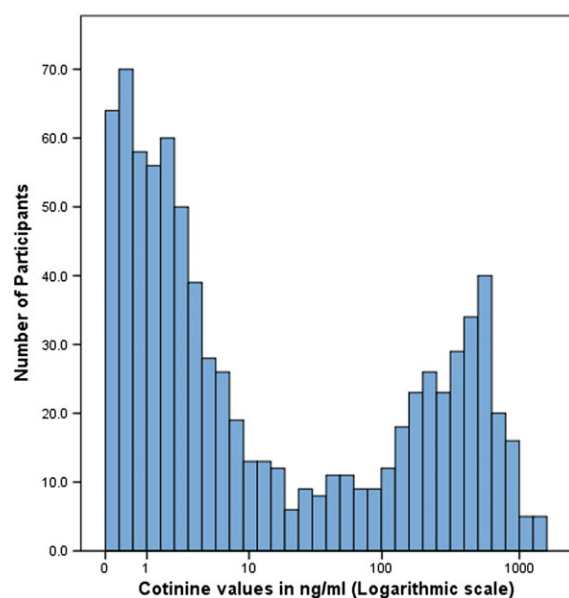


Figure 2 Distribution of cotinine values among self-reported quitters ($n = 822$). [Colour figure can be viewed at wileyonlinelibrary.com]

(see Table 1). Figure 2 presents the distribution of cotinine values in the sample, 5% ($n = 41$) had cotinine values below 0.15 ng/ml, the limit of sensitivity. Based on the widely used cut-point of 10 ng/ml, 57.8% of participants were verified quit (see Table 2) and using 15 ng/ml, 60.6% were verified quit (see Supporting information, Table S1).

Table 2 provides participant characteristics ($n = 822$) by cotinine verification status using the 10 ng/ml cut-point. Participants with verified abstinence differed from participants who failed verification on several variables ($P < 0.05$). In univariate comparisons, participants who were older, female, white, had more than a high school education and provided the saliva sample by mail (versus in person) were more likely to validate self-reported quitting. Participants with Medicaid insurance (versus other insurance), had a smoking-related primary discharge diagnosis and were not continuously abstinent since hospital discharge were less likely to verify self-reported quitting. The proportions of participants who verified self-reported abstinence also differed by study site. Findings were similar using the 15 ng/ml cut-point, except that the difference by insurance type was non-significant.

We estimated multivariable logistic regression models using 10 and 15 ng/ml cut-points, adjusting for study site and including age, gender, race, ethnicity, education,

Table 2 Verification rates at 10 ng/ml by participant and study characteristics, univariate analyses ($n = 822$).

	<i>n</i>	% Verified abstinent	95% CI	<i>P</i> -value
All participants	822	57.8	54.4, 61.2	
Age (years)				0.002
18–44	147	50.2	44.4, 55.9	
45–64	263	60.9	56.3, 65.5	
≥ 65	64	67.4	57.9, 76.8	
Gender				0.025
Female	222	62.4	57.3, 67.4	
Male	251	54.6	50.0, 59.1	
Race				<0.001
White	299	64.9	60.5, 69.2	
African American	123	45.9	39.9, 51.9	
Other	53	57.0	46.9, 67.1	
Ethnicity				
Latino	56	57.1	47.3, 67.0	0.891
Education				0.020
≤ High school	249	54.2	49.7, 58.8	
> High school	225	62.3	57.3, 67.3	
Primary insurance				0.026
Medicaid	107	52.7	45.8, 59.6	
Other insurance	342	61.7	57.7, 65.8	
Admission through emergency room	284	56.1	51.8, 60.5	0.102
Live with smoker at 6-month follow-up	137	55.9	49.7, 62.1	0.880
Any of smoking disease groups: primary diagnosis	115	65.3	58.3, 72.4	0.022
Mental health disorder: primary diagnosis	7	58.3	30.4, 86.3	0.969
Mental health disorder: secondary diagnosis	211	56.3	51.2, 61.3	0.419
Abstinent since hospital discharge	325	68.3	64.1, 72.5	<0.001
Treatment arm assignment				0.923
Intervention arm	253	57.6	53.0, 62.3	
Control arm	222	58.0	53.0, 62.9	
Saliva collection method				<0.001
In person	49	32.2	24.8, 39.7	
Mailed	426	63.6	59.9, 67.2	
Study site				<0.001
New York	71	50.7	42.4, 59.0	
Alabama	128	48.9	42.8, 54.9	
California	30	42.3	30.7, 53.8	
Kansas	193	67.0	61.6, 72.5	
Massachusetts	53	86.9	78.4, 95.4	

CI = confidence interval.

insurance (Medicaid versus other), admission type (emergency room versus other), primary discharge diagnoses (smoking-related disease; mental health disorder), secondary mental disorder diagnosis, continuous abstinence since hospital discharge, intervention treatment assignment, sample collection method (mailed versus in person) and an interaction term between treatment assignment and sample collection method (see Table 3). We included this interaction due to the differences in verification rates by collection method. Using the 10 ng/ml cut-point, the treatment assignment by sample collection method interaction was non-significant [adjusted odds ratio (AOR) = 1.34, 95% confidence interval (CI) = 0.58, 3.13, $P = 0.495$], therefore we report the model results without this effect.

Participants who had education beyond high school, were continuously abstinent since hospitalization and who mailed their sample were more likely to verify self-reported abstinence biochemically. Compared to white participants, African American participants were less likely to be cotinine-verified quit. The odds of cotinine verification did not differ by treatment arm. The interaction term between treatment assignment and sample collection method was also non-significant in the logistic regression model for cotinine verification at the 15 ng/ml cut-point (AOR = 1.37, 95% CI = 0.58, 3.20, $P = 0.472$) and overall findings were similar to the 10 ng/ml model.

Table 4 presents cotinine values (median, interquartile ranges, ranges) and cotinine verification rates for all

Table 3 Results from logistic regression models for cotinine-verified self-reported abstinence.

	10 ng/ml cotinine			15 ng/ml cotinine		
	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
Age (years)						
45–64 versus 18–44	1.09	0.57, 2.08	0.797	0.74	0.37, 1.48	0.392
≥ 65 versus 18–44	1.34	0.74, 2.42	0.336	0.97	0.51, 1.84	0.914
Gender						
Female versus male	1.24	0.88, 1.73	0.218	1.31	0.93, 1.86	0.123
Race						
African American versus white	0.64	0.44, 0.93	0.019	0.59	0.41, 0.87	0.007
Other race versus white	0.75	0.40, 1.40	0.374	0.76	0.40, 1.45	0.404
Latino	1.23	0.65, 2.32	0.524	1.14	0.59, 2.19	0.696
Education						
> High school versus ≤ high school	1.51	1.07, 2.11	0.018	1.71	1.20, 2.43	0.003
Insurance						
Medicaid versus other	0.85	0.58, 1.25	0.420	1.03	0.70, 1.52	0.881
Admission through emergency room versus admission	0.82	0.56, 1.19	0.288	0.90	0.62, 1.32	0.601
any of smoking disease groups: primary diagnosis	1.11	0.72, 1.70	0.643	1.14	0.73, 1.79	0.557
Mental health disorder: primary diagnosis	1.09	0.30, 4.02	0.897	1.53	0.38, 6.13	0.548
Mental health disorder: secondary diagnosis	0.94	0.62, 1.42	0.766	0.96	0.63, 1.47	0.849
Continuous abstinence since hospital discharge	2.82	2.02, 3.94	<0.001	3.28	2.32, 4.64	<0.001
Treatment arm						
Intervention versus control	1.14	0.82, 1.58	0.440	1.13	0.81, 1.59	0.474
Saliva collection methods						
Mailed versus in person	3.20	1.96, 5.21	<0.001	3.35	2.04, 5.50	<0.001

Logistic regressions adjusted for study site. Due to missing data, analyses were conducted on 750 participants. Statistically significant odds ratios are shown in bold type. CI = confidence interval.

Table 4 Cotinine verification status among participants reporting 7-day point prevalence abstinence at 6 month follow-up.

	Sample size		Cotinine value (ng/ml)		Cotinine verified (10 ng/ml)	Cotinine verified (15 ng/ml)
	n	Median	Interquartile range	Range	% (95% CI)	% (95% CI)
All Participants	822	4.7	185	0–1561	57.8 (54.4, 61.2)	60.6 (57.2, 63.9)
Subset who returned survey to report on their tobacco use status with saliva sample (n = 618)	618	5.3	183	0–1561	56.5 (52.6, 60.4)	59.2 (55.3, 63.1)
All respondents	618	5.3	183	0–1561	56.5 (52.6, 60.4)	59.2 (55.3, 63.1)
Report 7-day abstinence from tobacco and NRT	435	2.4	7	0–1558	77.2 (73.3, 81.2)	81.1 (77.5, 84.8)
Report 7-day use of tobacco or NRT	183	320.1	400	0–1561	7.1 (3.4, 10.8)	7.1 (3.4, 10.8)
Subset with a completed survey at sample collection who reported abstinence from tobacco and no nicotine product use in the past 7 days (n = 435)	435	2.4	7	0–1558	77.2 (73.3, 81.2)	81.1 (77.5, 84.8)
No past 24-hour SHS	218	1.5	3	0–1083	88.1 (83.8, 92.4)	92.2 (88.6, 95.8)
Past 24-hour SHS	217	3.8	23	0–1558	66.4 (60.0, 72.7)	70.0 (63.9, 76.2)

SHS = secondhand smoke (SHS); NRT = nicotine replacement therapy; CI = confidence interval.

participants and for subgroups. Among the four study sites that repeated their assessment of past 7-day smoking status at the time of saliva collection (n = 653), 168 (25.73%) of those who reported abstinence at 6-month follow-up reported smoking in the 7 days prior to saliva collection. Among the 618 participants in three studies

that were asked about other nicotine exposure in the 7-days prior to saliva collection, 43 (7.0%) reported other tobacco or e-cigarette use and 39 (6.3%) reported NRT use; 367 (59.4%) also reported that they had been exposed to indoor second-hand smoke in the past 24 hours.

DISCUSSION

This study examined biochemical verification rates of self-reported smoking abstinence in five smoking cessation randomized clinical trials that enrolled smokers at hospitalization. Among self-reported quitters at 6-month follow-up, analysis of salivary cotinine using the widely accepted cut-point of 10 ng/ml yielded a 58% verification rate. Thus, approximately 42% of participants who self-reported abstinence failed verification. We found a bimodal distribution of cotinine values consistent with samples including both non-smokers and active smokers [11,26,27]. Two demographic factors (African American race and lower education), one study procedural factor (in-person sample collection) and one quitting experience factor (non-continuous cessation) were associated significantly with a decreased likelihood of verifying self-reported smoking status.

Similar to findings from the parent trials, our results showed that the likelihood of verifying abstinence was not related to treatment group. Each parent trial found that sample return rates and verification rates were the same across the intervention and control study arms, and that verified abstinence paralleled self-report [14–18]. For the field of tobacco research, this finding raises a key methodological question: when are the time, costs and limitations of biochemical verification justified in research trials whose goal is to assess the efficacy of an intervention compared to a control condition?

Sample collection method was associated with verification rate even after taking into account demographic and smoking-related variables. Three of the five trials included in these analyses also collected in-person samples. The two studies with the highest proportions of in-person samples provided more appealing participant incentives (e.g. cash versus check) for in-person verification, and this may have increased the likelihood that even participants who relapsed or misreported followed through to provide a sample. Verification rate variation also may have resulted from differences in the study populations due to regional culture, proportion of minorities, population density or other factors that differed between study sites.

Most of the saliva samples in this study were returned via mail. Four trials provided a survey to repeat the self-reported assessment of tobacco use in the mailed kits. We found that one in four of the participants returning this survey with their sample reported smoking in the past 7 days. This suggests that these participants either misreported at the outcome survey or relapsed between the time they completed the survey and received the collection kit. A smaller proportion reported using other tobacco, e-cigarettes or NRT in the past 7 days. These admissions indicate that some discrepant results could occur potentially as a result of relapse to smoking or other nicotine exposure during the interim

between reporting smoking status and providing a sample for verification. Participants who denied using tobacco or nicotine products on the mailed survey had a higher rate of cotinine-verified abstinence (77%). Further, participants who indicated that they had not smoked but were exposed to second-hand cigarette smoke in the past 24 hours had lower rates of verification than those who indicated no exposure. Given the range of cotinine values for second-hand smoke-exposed participants, many who failed verification in this subset were likely to be active smokers [27].

Race and education were the only demographic variables associated with verification when controlling for other characteristics. Perhaps these differences by race and education reflect a variation in response to the demand characteristics of being in a smoking cessation trial or simply wanting to avoid stigma that may be associated with continued smoking. However, the reasons that these variables impacted verification rates are unclear.

Previous recommendations for smoking cessation trials have included proposals for assessing continuous or prolonged smoking abstinence as the standard outcome [1,2]. Our analyses showed that controlling for individual and study-level characteristics, participants who reported that they remained abstinent since their hospitalization were more likely to be cotinine-verified abstinent at 6-month follow-up. The fact that participants with prolonged abstinence have higher verification rates suggests that prolonged abstinence may be a better indicator of long-term smoking cessation success. However, approximately 30% of participants reporting prolonged abstinence failed verification. This suggests that verification has potential utility even for longer time-frames.

The current study makes an important contribution to the ongoing scientific dialogue regarding biochemical verification of smoking abstinence by including findings from five large clinical trials with hospitalized smokers. Study strengths include using data from several regions within the United States and from a variety of hospitals. Study sites collaborated at the beginning of the trials to ensure standard sample collection and processing procedures. However, there are several limitations. Saliva samples were analyzed using EIA methods rather than the better-performing liquid or gas chromatographic methods [19,21]. However, the range and distribution of cotinine values appears similar to data from population-based studies using chromatographic assays methods [25,26]. We were unable to determine whether the reason for failed verification was due solely to misreporting or excessive second-hand smoke exposure. Sample collection was not observed directly for mailed samples. The return rate of 70% for usable saliva samples is consistent with evaluations from population-based, low-intensity trials [28]; however, the fact that 30% of participants did not have samples available for verification remains a limitation.

In conclusion, throughout five large clinical trials of smoking cessation interventions, only approximately 60% of participants reporting not smoking validated that self-report with cotinine levels consistent with smoking abstinence. This underscores that self-report measures are likely to result in inflated smoking cessation rates within this population. Further, when collecting mailed samples for cotinine testing, researchers should explore the utility of including a survey to reduce discrepancies in self-report. Future studies that explore reasons for discrepant reporting and how this source of error can be minimized are also warranted.

Clinical trial registration

ClinicalTrials.gov NCT01177176 (NAR), NCT01277250 (KFH), NCT01289275 (SHZ), NCT01305928 (KPR), and NCT01363245 (SES).

Declaration of interests

K.P.R. has received clinical trial medications from Niconovum. N.A.R. has been an unpaid consultant for Pfizer and receives royalties from UpToDate.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

Table S1 Verification rates at 15 ng/ml by participant and study characteristics, univariate analyses ($n = 822$).