31. Lara M.C., Weiss B., Illa I. et al. Infusion of platelets transiently reduces nucleoside overload in MNGIE. Neurology. 2006;67:1461–1463.
32. Hirano M., Marti R., Casali C. et al. Allogeneic stem cell transplantation corrects biochemical derangements in MNGIE. Neurology. 2006;67:1458–1460.
33. Marti R., Verschuuren J.J., Buchman A. et al. Late-onset MNGIE due to partial loss of thymidine phosphorylase activity. Ann Neurol. 2005;58:649–652.
34. Nishigaki Y., Marti R., Copeland W.C., Hirano M. Site-specific somatic mitochondrial DNA point mutations in patients with thymidine phosphorylase deficiency. J Clin Invest. 2003;111:1913–1921.
35. Taanman J.W., Daras M., Albrecht J. et al. Characterization of a novel TYMP splice site mutation associated with mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) Neuromuscul Disord. 2009;19:151–154.

BIOCHEMICAL METHODS OF SMOKING STATUS VERIFICATION IN TOBACCO RESEARCH

Kravchenko V.M.[1], Nodar Sulashvili[2], Benzid Yassine[3]
[1]National University of Pharmacy, Kharkiv, Ukraine
[2]Tbilisi State Medical University
[3]Master of Pharmacy, Agadir, Kingdom of Morocco
biochem@nupn.edu.ua

Abstract. Increasing digital delivery of smoking cessation interventions has resulted in the need to employ novel strategies for remote biochemical verification. This scoping review and meta-analysis aimed to investigate best practices for remote biochemical verification of smoking status. The scientific literature was searched for studies that reported remotely obtained (not in-person) biochemical confirmation of smoking status (ie, combustible tobacco). A meta-analysis of proportions was conducted to investigate key outcomes, which included rates of returned biological samples and the ratio of biochemically verified to self-reported abstinence rates. A total of 82 studies were included. The most common samples were expired air (46%) and saliva (40% of studies), the most common biomarkers were carbon monoxide (48%) and cotinine (44%), and the most common verification methods were video confirmation (37%) and mail-in samples for lab analysis (26%). Mean sample return rates determined by random-effects meta-analysis were 70% for smoking cessation intervention studies without contingency management (CM), 77% for CM studies, and

65% for other studies. Among smoking cessation intervention studies without CM, self-reported abstinence rates were 21%, biochemically verified abstinence rates were 10%, and 47% of individuals who self-reported abstinence were also biochemically confirmed as abstinent. This scoping review suggests that improvements in sample return rates in remote biochemical verification studies of smoking status are needed. Recommendations for reporting standards are provided that may enhance confidence in the validity of reported abstinence rates in remote studies.

Keywords: biochemical verification methods, smoking status, tobacco, carbon monoxide, cotinine

Introduction. Biochemically verified smoking status is widely considered the "gold standard" outcome in smoking cessation research [1, 2]. However, the remote delivery of interventions and collection of cessation outcome data has become increasingly common [3, 4] and the COVID-19 pandemic with associated limitations on in-person research has only accelerated the -importance of remote interventions. In remote studies, participants do not attend in-person sessions with study personnel and interventions are delivered and data are collected via telephone, mobile application, the Internet, social media, and/or other virtual methods [4-8]. Remote biochemical verification of abstinence in these studies presents many opportunities and challenges for tobacco researchers.

Previous recommendations suggested that biochemical verification of smoking abstinence is not necessary for remote studies [9]. The assumption was that participants might be less pressured to provide socially desirable responses if they do not encounter study staff or treatment providers at follow-up face-to-face. However, more recent recommendations suggest the need for biochemical verification of abstinence in all cessation studies while also acknowledging that biochemical verification may not be possible for all types of study designs. Currently, little is known about which methods of biochemical verification are most feasible and accurate when delivered remotely, how remotely biochemically verified abstinence rates compare to self-reported abstinence, or how to improve adherence to remote biochemical collection.

The primary focus of this paper is on the biochemical verification of smoking abstinence as the primary study outcome. In some studies where the primary outcome was not specified, the final assessment point that included biochemical verification of smoking status was selected. Because the goal of the current study was to conduct an inclusive scoping review, the use of biochemical verification for other purposes (eg, feasibility studies) is also briefly discussed.

The aim of the study. This scoping review and meta-analysis aimed to investigate best practices for remote biochemical verification of smoking status.

Materials and Methods. The scientific literature was searched for studies that reported remotely obtained biochemical confirmation of smoking status. A meta-analysis of proportions was conducted to investigate key outcomes, which included rates of returned biological samples and the ratio of biochemically verified to self-reported abstinence rates.

The databases were searched: Ovid, Medline; Wiley, Cochrane Central Register of Controlled Trials; Elsevier, Embase; Clarivate, Web of Science; Cumulative Index of Nursing and Allied Health Literature and PsycInfo.

Descriptive statistics were used to report study characteristics. Then, a series of random-effects meta-analyses of proportions were conducted to estimate the percentage rates of returned samples for all study types. Because of heterogeneity in study design, this review did not make comparisons across study types. Self-reported, biochemically verified, and the concordance between biochemically verified and self-reported abstinence rates were only investigated among smoking cessation intervention studies excluding CM, because CM studies did not report self-reported abstinence rates, and the study designs among other studies were too heterogeneous to allow for meaningful comparisons. Meta regressions were estimated to investigate relationships between study characteristics (eg, samples collected, biomarkers, or verification method) and study outcomes (eg, sample return rates).

Results and Discussion. Of all smoking cessation intervention studies (excluding CM), (71%) reported collecting saliva cotinine as the primary sample to remotely biochemically verify smoking status. Eight (19%) studies used expired-air carbon monoxide, three (7%) studies used urine cotinine, two (5%) studies used saliva cotinine as well as anabasine, and one (2%) study used blood as well as saliva cotinine. The most frequent verification method used was mail-in samples which were lab analyzed (43%). Other verification methods used were both mail-in and in-person samples (eg, studies used remote collection methods if participants lived far from the study site, were unable to attend study visits in person, etc) (17%), video confirmation (14%), apps (10%), photo (7%), and mail-in test strips (5%).

Biochemical verification in these studies was conducted primarily by evaluating expired-air carbon monoxide (43%), followed by saliva cotinine testing (21%). In one study (10%) collected hair/nail samples without any biomarker or analysis reported. Studies in this category used various verification methods to confirm sample results, including combinations of multiple methods (21%), apps (21%), mail-in samples (lab

analyzed) (21%), photos (14%), videos (14%), and both mail-in and in-person samples for lab analysis (7%).

The goal of the current study was to conduct a scoping review and meta-analysis of studies using remote biochemical verification of smoking status. A total of 82 studies were included. Among the 42 non-CM smoking cessation intervention studies, the most common type of sample collected was saliva (71% of studies), the most common biomarker used was cotinine (76% of studies), and the most common verification method was lab analysis of mailed samples (43% of studies). CM studies and other studies most commonly collected expired air (92% of CM studies; 43% of other studies), used carbon monoxide (92% of CM studies; 50% of other studies), and video verification (85% of CM studies). Mean sample return rates determined by random-effects meta-analysis were 70% for smoking cessation intervention studies without CM, 77% for CM studies, and 65% for other studies. Approaches to increase participant adherence to returning samples reported among studies were not significantly related to higher sample return rates. Among smoking cessation intervention studies without CM included in meta-analysis, self-reported abstinence rates were 21%, and biochemically verified abstinence rates were 10%.

Overall, the current review found a mismatch between self-reported and biochemically verified abstinence rates in smoking cessation intervention studies without CM that employed remote biochemical verification. Regarding the ratio of biochemically verified to self-reported outcomes, only 47% of self-reported abstainers were confirmed in pooled random-effects meta-analysis. This ratio did not significantly vary across studies collecting different types of samples or using different biomarkers. However, studies that used video confirmation had a significantly higher ratio compared to studies that used photo confirmation, mail-in samples for lab analysis, or mail-in samples for lab analysis combined with in-person samples. Our findings on the mismatch between self-reported and biochemically verified abstinence are in line with previously reported findings. A recent study [10] combined data from five hospital-initiated smoking cessation trials and found that 60% of self-reported smoking cessation was biochemically confirmed, which is slightly higher than the confirmation rates found in the current study. In sum, these findings suggest that remotely biochemically verified abstinence rates are substantially lower than self-reported abstinence rates and are therefore not comparable across studies. The reasons why study participants who self-reported abstinence did not provide biochemical confirmation remain unknown and may plausibly include lack of convenience,

additional burdensome effort, uncomfortable or tedious procedures, as well as continued smoking and/or relapse.

This review also found no significant relationships between methods to improve adherence and return rates. On the one hand, these findings suggest the need to identify ways to improve return rates of samples for remote biochemical verification across the board. For example, new, low-cost remote CO verification devices are increasingly available and could be used more widely to assess smoking abstinence [11, 12]. Moreover, studies could experimentally test different biochemical verification approaches and methods to improve participant adherence. On the other hand, studies using remote biochemical verification should report in detail testing procedures and relevant data, including sample return rates and number of usable samples by study group/condition, as well as approaches used to improve participant adherence. Moving forward, improving remote biochemical verification procedures will be a critical contribution to digital and mobile health smoking cessation studies and other studies that deliver remote smoking cessation support.

Finally, not all remote verification methods can confirm that the participant provides the sample instead of a third person. Confirmation of identity is likely more important for CM studies that directly tie abstinence to distribution of rewards and thus may create an incentive for participants to -misrepresent who provided the sample. CM studies most frequently use video confirmation of breath sample provision, for example, videos that are automatically uploaded to a platform and can be checked by research staff [13]. More recently, studies have also used photos were taken during the breath sample provision process [14], including automatic facial recognition technology [11]. Another strategy to confirm participant identity, used by some smoking cessation intervention studies that do not rely on frequent sampling of abstinence, includes real-time video calls with participants and project staff, which has been used for both breath CO [15] and saliva cotinine (using test strips) [16] monitoring. A technique that does not require real-time contact with participants includes mailing saliva cotinine test kits to participants, paired with the request to document the sample provision and test results with photos to be sent to research staff [17, 18]. Thus, multiple different approaches are available to confirm if participants provide samples for biochemical verification themselves**.**

Conclusions. This scoping review and meta-analysis provide an overview of studies that used remote biochemical verification of smoking status. The review found that biochemically verified abstinence rates were lower than self-reported abstinence rates for almost all studies included. However, in light of limitations to data available

from included studies, it remains unclear which factors are responsible for this mismatch and if the ground truth of smoking abstinence is more closely represented by biochemically verified or self-reported rates in remote studies. In addition to recent recommendations for biochemical verification provided by our SRNT colleagues,1 and to improve the evidence for remote biochemical verification of smoking status, the authors recommend the following reporting guidelines for future studies in this area: report sample return rates, usable samples, self-reported abstinence, biochemically verified abstinence, and the number of concordant/discordant self-reported and verified outcomes, with detailed data reported for each study subgroup/condition. Report and account for other tobacco product use and cannabis use. Report identity verification of who provided samples, and include and report study approaches to increase sample return rates. The results of this review suggest that improved verification methods and improved reporting standards are needed to enhance confidence in the validity of reported abstinence rates in remote studies.

References

1. Benowitz N.L., Bernert J.T., Foulds J. et al. Biochemical verification of tobacco use and abstinence: 2019 update. Nicotine Tob Res. 2020;22(7):1086–1097.
2. Piper M.E., Baker T.B., Benowitz N.L. et al. E-cigarette dependence measures in dual users: reliability and relations with dependence criteria and e-cigarette cessation. Nicotine Tob Res. 2020;22(5):756–763.
3. Prutzman Y.M., Wiseman K.P., Grady M.A. et al. Using digital technologies to reach tobacco users who want to quit: evidence from the national cancer institute's smokefree.gov initiative. Am J Prev Med. 2021;60(3 suppl 2):S172–S184.
4. Whittaker R., McRobbie H., Bullen C. et al. Mobile phone text messaging and app-based interventions for smoking cessation. Cochrane Database Syst Rev. 2019;10(10):CD006611.
5. Cummins S.E., Bailey L., Campbell S. et al. Tobacco cessation quitlines in North America: a descriptive study. Tob Control. 2007;16(suppl 1):i9–15.
6. Graham A.L., Carpenter K.M., Cha S. et al. Systematic review and meta-analysis of Internet interventions for smoking cessation among adults. Subst Abuse Rehabil. 2016;7:55–69.
7. Ramo D.E, Thrul J., Delucchi K.L. et al. A randomized controlled evaluation of the tobacco status project, a Facebook intervention for young adults. Addiction. Published online May 2018;113(9):1683–1695.

8. Goldenhersch E., Thrul J., Ungaretti J. et al. Virtual reality smartphone-based intervention for smoking cessation: pilot randomized controlled trial on initial clinical efficacy and adherence. J Med Internet Res. 2020;22(7):e17571–e17571.
9. Verification SS on B. Biochemical verification of tobacco use and cessation. Nicotine Tob Res. 2002;4(2):149–159.
10. Scheuermann T.S., Richter K.P., Rigotti N.A. et al. Accuracy of self-reported smoking abstinence in clinical trials of hospital-initiated smoking interventions. Addiction. 2017;112(12):2227.
11. Kendzor D.E., Businelle M.S., Waring J.J.CC. et al. Automated mobile delivery of financial incentives for smoking cessation among socioeconomically disadvantaged adults: feasibility study. JMIR Mhealth Uhealth. 2020;8(4):1–13.
12. Patrick H., Fujii C.A., Glaser D.B. et al. A comprehensive digital program for smoking cessation: assessing feasibility in a single-group cohort study. JMIR Mhealth Uhealth. 2018;6(12):e117081–e117015.
13. Dallery J., Meredith S., Jarvis B., Nuzzo P.A. Internet-based group contingency management to promote smoking abstinence. Exp Clin Psychopharmacol. 2015;23(3):176–183.
14. Dallery J., Stinson L., Bolívar H. et al. mMotiv8: a smartphone-based contingency management intervention to promote smoking cessation. J Appl Behav Anal. 2021;54(1):38–53.
15. Free C., Whittaker R., Knight R. et al. Txt2stop: a pilot randomised controlled trial of mobile phone-based smoking cessation support. Tob Control. 2009;18(2):88–91.
16. Kim S.S., Sitthisongkram S., Bernstein K. et al. A randomized controlled trial of a videoconferencing smoking cessation intervention for Korean American women: preliminary findings. Int J Womens Health. 2016;8:453–462.
17. Meacham M.C., Ramo D.E., Prochaska J.J. et al. A Facebook intervention to address cigarette smoking and heavy episodic drinking: a pilot randomized controlled trial. J Subst Abuse Treat. 2021;122:108211.
18. Hrul J., Meacham M., Ramo D. A novel and remote biochemical verification method ofsmoking abstinence: predictors of participant compliance. Tob Prev Cessat. 2018;4(May):1–5.