

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	A cross-sectional study on the awareness, susceptibility, and use of heated tobacco products among adolescents in Guatemala City, Guatemala
<b>AUTHORS</b>	Gottschlich, Anna; Mus, Sophia; Monzon, Jose Carlos; Thrasher, James; Barnoya, Joaquin

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Arielle Selya Sanford Research, USA
<b>REVIEW RETURNED</b>	12-Jun-2020

<b>GENERAL COMMENTS</b>	<p>This study examines the awareness, susceptibility and use of heated tobacco products (HTP) in high school students in Guatemala. The authors find that about half of youth are aware of HTPs, about half are susceptible, but use remains low. The risk factors include use of other nicotine products and other substances. HTP use is not a gateway to nicotine use, as they are almost never the first nicotine product used. This study represents one of the very few studies on alternative tobacco product use in low- and middle- income countries where restrictions are loose. There are several limitations to this study that limit its interpretability and generalizability</p> <p>Major comments:</p> <ol style="list-style-type: none"><li>1. An important issue that is not addressed in the manuscript is the risk profile of HTP's. The Public Health England 2018 report estimates that e-cigarettes are only 5% as harmful as conventional cigarettes, and I believe the estimates for HTP are similar. This is essential when examining different types of nicotine products, as it makes sense to focus more efforts to reduce use of the more dangerous products.</li><li>2. Parts of the manuscript, including the abstract, seem inappropriately alarmist against HTP's. For example: (in the abstract) "Prevention and intervention strategies could target adolescents who use other substances..." Of all the products that were assessed in this questionnaire, HTP's and e-cigarettes are the lowest-risk. It is not sensible to screen based on the riskier substance, and intervene on the minimal-risk substance. To the manuscript's credit, it states that HTP's are unlikely to be a gateway since they are almost never the first product used; however, I don't find any of the findings to be alarming. HTP's have wide awareness in Guatemala but usage remains low.</li><li>3. More details of the survey design and study participants are needed. How were the 30 invited schools selected? Were there</li></ol>
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	<p>significant differences between school that agree to participate and those who refused? Were all students in the participating schools invited to take the survey or chosen based on criteria? Was any incentive given for the participation?</p> <p>4. Regression models include 20 independent variables for each dependent variable, which makes the multicollinearity and overfitted model highly likely. It would be helpful to see correlations between the independent variables to assess this.</p> <p>5. The information presented in the Tables is confusing and in places inaccurate:</p> <ul style="list-style-type: none"> <li>- Table 1: Combining N and Mean in one column and %/SD in another column is confusing. I suggest grouping Mean and % in the same column, as these are both point estimates for the measure of central tendency, and N and SD both quantify the certainty around that estimate. Second, it takes a long time to figure out which set of statistics each variable is; this could be helped by including the “%” in the relevant cells.</li> <li>- Presumably, an adolescent must be aware of HTP’s to be susceptible to it. Since the values are almost identical (1503 and 1500) in Table 1, does this mean everyone who’s aware is susceptible? Or is it that some are willing to use HTP’s even if they are not aware of them? Some interpretation of this is necessary.</li> <li>- Tables 2 and 3: An * indicates statistical significant at <math>p &lt; 0.05</math>. However this does not seem at all correct. The cells marked by * do not always have a 95% confidence interval that excludes 1; and there are many cells whose confidence interval does exclude 1 that are not marked with a *.</li> </ul> <p>6. Page 17, line 13: Reference 13 is based on a nationally representative study in Korea, which has a GDP per capita of \$31,000 compared to Guatemala whose GDP per capita is \$4,549. As the majority of Guatemalan high school students attend private school and authors did not provide specific information on the sample’s socioeconomic status, higher socioeconomic status of this sample doesn’t really explain this discrepancy.</p> <p>Minor comments:</p> <ol style="list-style-type: none"> <li>1. Page 13, line 24: “Nearly two-thirds (58.4%)” is an overstatement. 58.4% is slightly more than half, not nearly two-thirds.</li> <li>2. Page 16, lines 29-35: the level of awareness and susceptibility numbers from Canada, US, UK do not have a reference.</li> <li>3. Page 16, line 49: If a theory is to be used to support authors’ argument (Jessor’s Problem Behavior Theory), it should have been discussed from the Introduction section and reflected on the initial study/survey design.</li> </ol>
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<b>REVIEWER</b>	Ai Hori University of Tsukuba, Japan
<b>REVIEW RETURNED</b>	01-Jul-2020

<b>GENERAL COMMENTS</b>	This study has revealed the factors associated with heated tobacco product use among adolescents in recent Guatemala.
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	<p>Despite a few limitations about the study design, the result is informative to the future HTP use prevention for the young generation.</p> <p>Comments:</p> <p>#1 Table 2 and Table 3 The adjusted odds ratio for “friend uses e-cigarettes” in Table 2 and 3, and “Bachillerato (grades 10-12)” in Table 3 seems strange as compared to unadjusted odds ratio. The variable seems to have multicollinearity with other variables, or, might have other statistical problems. Please reconsider the statistical model and discuss the result with the caution.</p> <p>#2 P14 L1-2 Concerning friend cigarette or e-cigarette use, the corresponding percentages were ... → Concerning friend cigarette, e-cigarette, or “HTPs” use, the corresponding percentages were ...</p>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Arielle Selya

Institution and Country: Sanford Research, USA

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

This study examines the awareness, susceptibility and use of heated tobacco products (HTP) in high school students in Guatemala. The authors find that about half of youth are aware of HTPs, about half are susceptible, but use remains low. The risk factors include use of other nicotine products and other substances. HTP use is not a gateway to nicotine use, as they are almost never the first nicotine product used. This study represents one of the very few studies on alternative tobacco product use in low- and middle- income countries where restrictions are loose. There are several limitations to this study that limit its interpretability and generalizability.

Thank you for your comments and suggestions to improve this work.

Major comments:

1. An important issue that is not addressed in the manuscript is the risk profile of HTP’s. The Public Health England 2018 report estimates that e-cigarettes are only 5% as harmful as conventional cigarettes, and I believe the estimates for HTP are similar. This is essential when examining different types of nicotine products, as it makes sense to focus more efforts to reduce use of the more dangerous products.

Thank you very much for your comment. To the best of our knowledge, it is yet unknown the potential harmful effect of HTP. We have added a sentence:

“However, current evidence on the harmful effects of HTPs compared to conventional cigarettes are yet to be determined as most of the available evidence is in vitro and comes from tobacco industry funded research.”

2. Parts of the manuscript, including the abstract, seem inappropriately alarmist against HTP’s. For

example: (in the abstract) “Prevention and intervention strategies could target adolescents who use other substances...” Of all the products that were assessed in this questionnaire, HTP’s and e-cigarettes are the lowest-risk. It is not sensible to screen based on the riskier substance, and intervene on the minimal-risk substance. To the manuscript’s credit, it states that HTP’s are unlikely to be a gateway since they are almost never the first product used; however, I don’t find any of the findings to be alarming. HTP’s have wide awareness in Guatemala but usage remains low. While we do believe more research is required to sufficiently understand the risks of HTPs, we have modified the following sentences to try to reduce the implied risk of use:

Abstract:

“Tobacco prevention and intervention strategies for cigarettes and e-cigarettes should now also include HTPs, which tend to be used by similar adolescent populations (i.e. those who use other substances or are exposed to tobacco through family and friends).”

Introduction:

“Therefore, this study aims to address this gap by evaluating the prevalence and correlates of HTP awareness, susceptibility, and use among adolescents in Guatemala to inform prevention and intervention strategies to target those at highest risk for tobacco use, including use of HTPs.”

Methods:

“Results of this study will be shared with enrolled schools and support will be granted to develop and tailor tobacco-use control strategies.”

3. More details of the survey design and study participants are needed. How were the 30 invited schools selected? Were there significant differences between school that agree to participate and those who refused? Were all students in the participating schools invited to take the survey or chosen based on criteria? Was any incentive given for the participation?

The following has been added into the methods section:

“Based on the official list of private and public schools in Guatemala City, 30 private schools were conveniently selected from middle to high socioeconomic urban areas and sent invitation letters to participate in the study. Six of these schools declined, four of which enrolled only boys or girls and 14 did not respond, leaving 10 participating schools.”

“All students in participating grades were invited to complete the survey and no incentive was given to the participants or schools.”

4. Regression models include 20 independent variables for each dependent variable, which makes the multicollinearity and overfitted model highly likely. It would be helpful to see correlations between the independent variables to assess this.

To address any issues with multicollinearity, we calculated the variance inflation factor (VIF) for each variable across models. The majority of variables had a VIF between 1 and 2 and the highest VIF was 3.02, demonstrating no issues with collinearity. The following was added to the methods:

“In all models, we evaluated collinearity among independent variables by examining the variance inflation factor, and results indicated no collinearity concerns.”

5. The information presented in the Tables is confusing and in places inaccurate:

- Table 1: Combining N and Mean in one column and %/SD in another column is confusing. I suggest grouping Mean and % in the same column, as these are both point estimates for the measure of central tendency, and N and SD both quantify the certainty around that estimate. Second, it takes a long time to figure out which set of statistics each variable is; this could be helped by

including the “%” in the relevant cells.

To improve readability, the heading for “dependent variables”, “socio-demographic characteristics”, and “substance use variables” now reads “N” in the first column and “%” in the second. The only row including the mean and SD is the age variable and is noted with an Asterisk and footnote. The heading for “constructed scales (score range) now reads “Mean” in the first column and “SD” in the second.

- Presumably, an adolescent must be aware of HTP’s to be susceptible to it. Since the values are almost identical (1503 and 1500) in Table 1, does this mean everyone who’s aware is susceptible? Or is it that some are willing to use HTP’s even if they are not aware of them? Some interpretation of this is necessary.

The way the survey was structured, a student did not need to be aware of HTPs to be susceptible. The survey first asked if a student had ever heard of HTPs (and showed a picture and description of the product). Then it asked if they would use the HTP if offered by a friend. In this population, 939 students were both aware of and susceptible to HTPs, 802 were neither aware nor susceptible, 563 were aware and not susceptible, and 560 were not (previously) aware and were susceptible.

The following has been added to the methods:

“We first assessed HTP awareness (yes, no) by showing an image and description of an IQOS, the only HTP available Guatemala, and asking if they had previously heard of them. Susceptibility to future HTP use was then assessed for all participants with a single question adapted from Pierce et al.’s validated scale...Students did not need to be previously aware of HTPs to be susceptible to future use.”

And the results:

“In this sample, 939 (32.7%) students were both previously aware of HTPs and susceptible to future use, while 802 (27.9%) were neither previously aware nor susceptible to future use. Furthermore, 563 (19.6%) were previously aware but not susceptible, and 560 (19.5%) were not previously aware but were susceptible.”

- Tables 2 and 3: An \* indicates statistical significant at  $p < 0.05$ . However this does not seem at all correct. The cells marked by \* do not always have a 95% confidence interval that excludes 1; and there are many cells whose confidence interval does exclude 1 that are not marked with a \*.

Thanks for catching this, the error has now been corrected in Tables 2 and 3.

There was also a small error in the coding, which has now been corrected, that slightly changed the point estimates and confidence intervals for the “current HTP use” model, but did not change significance of covariates.

6. Page 17, line 13: Reference 13 is based on a nationally representative study in Korea, which has a GDP per capita of \$31,000 compared to Guatemala whose GDP per capita is \$4,549. As the majority of Guatemalan high school students attend private school and authors did not provide specific information on the sample’s socioeconomic status, higher socioeconomic status of this sample doesn’t really explain this discrepancy.

Most students specifically residing and attending school in Guatemala City (where the vast majority of the country’s wealth is located) attend private schools, but this is certainly not the case for the rest of the country. The families whose students attend one of this study’s participating schools are of higher SES than the majority of the country, leading us to the stated conclusion.

The following has been added to the discussion to make this point clearer:

While South Korea has a much higher GDP per capita than Guatemala, our study population was selected from private schools in middle and high SES neighborhoods in Guatemala City, which are predominantly attended by students of significant higher socioeconomic status, and this could be the

cause of the discrepancy. For example, the average monthly cost to attend one of the schools in our study is \$388-420USD plus an annual enrollment fee of on average \$550USD, and a 2020 report from the World Bank[38] found that about 50% of Guatemalans live below the upper-middle income poverty line of about \$165USD per month. However, according to the 2018 census, 37% of middle school students and 70% of high school students in Guatemala City attend private schools, so our results may be more generalizable to the rest of Guatemala City, but not the entire country.[39]

Minor comments:

1. Page 13, line 24: “Nearly two-thirds (58.4%)” is an overstatement. 58.4% is slightly more than half, not nearly two-thirds.

“Nearly two-thirds...” was changed to “Over half...”

2. Page 16, lines 29-35: the level of awareness and susceptibility numbers from Canada, US, UK do not have a reference.

Citation has been added.

3. Page 16, line 49: If a theory is to be used to support authors’ argument (Jessor’s Problem Behavior Theory), it should have been discussed from the Introduction section and reflected on the initial study/survey design.

The following has been added to the introduction:

“Although currently the correlates of HTP use among adolescents are relatively unknown, they may resemble those for e-cigarette use: male, current or ever smoker, having peers or parents who smoke, sensation seeking, and technophilia. Some of these factors are hypothesized to be related to e-cigarette use to due Jessor’s Problem Behavior Theory, which hypothesizes that engaging in one risky behavior increases the likelihood of engagement in other risky behaviors.”

And the methods:

“Sensation seeking (in accordance with Jessor’s Problem Behavior Theory) was evaluated with four items (i.e., “I would like to explore strange places”, “I like to do things that scare me”, “I like new and exciting experiences, even when I am breaking the rules”, and “Sometimes I do crazy things just for fun”) with Likert responses (1=strongly disagree; 5=strongly agree) and averaged together (alpha = 0.77).”

Reviewer: 2

Reviewer Name: Ai Hori

Institution and Country: University of Tsukuba, Japan

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

This study has revealed the factors associated with heated tobacco product use among adolescents in recent Guatemala. Despite a few limitations about the study design, the result is informative to the future HTP use prevention for the young generation.

Thank you for your comments and suggestions to improve this work.

Comments:

#1

Table 2 and Table 3

The adjusted odds ratio for “friend uses e-cigarettes” in Table 2 and 3, and “Bachillerato (grades 10-12)” in Table 3 seems strange as compared to unadjusted odds ratio. The variable seems to have multicollinearity with other variables, or, might have other statistical problems. Please reconsider the statistical model and discuss the result with the caution.

To address any issues with multicollinearity, we calculated the VIF for each variable across models.

The majority of variables had a VIF between 1 and 2 and the highest VIF was 3.02, demonstrating no issues with collinearity. The following was added to the methods:

“In all models, we evaluated collinearity among independent variables by examining the variance inflation factor, and results indicated no collinearity concerns.”

Furthermore, all significant results are described as “associated” with the outcome, with no claim of causation.

We agree that the adjusted odds ratio for “friend e-cigarette use” is unexpected. One possible explanation is that there is a perception that e-cigarettes are less harmful than HTPs. However, further research would be needed to substantiate that hypothesis.

#2

P14 L1-2 Concerning friend cigarette or e-cigarette use, the corresponding percentages were ...

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Concerning friend cigarette, e-cigarette, or “HTPs” use, the corresponding percentages were ...

Thank you, this has been corrected.

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Arielle Selya Pinney Associates, Inc., USA Sanford Research, USA  Between my initial review and my 2nd review of this manuscript, I became employed by Pinney Associates, Inc. which provides consulting services to JUUL on tobacco harm minimization.
<b>REVIEW RETURNED</b>	14-Sep-2020

<b>GENERAL COMMENTS</b>	This revision addressed several of my concerns, regarding the sample and its generalizability, the more thorough description of Jessor’s Problem Behavior Theory, and whether awareness of HTPs is necessary for susceptibility. The authors also made some appropriate changes relating to the possibly lower degree of risk of HTPs. I still have some remaining concerns: - Fundamentally, this manuscript seeks to intervene on youth HTP use, based on (among other things) other, riskier behaviors (e.g. cigarette smoking, binge drinking). Considering a central premise of this manuscript that risk factors cluster together, it seems to me that HTPs don’t warrant much concern for the following reasons: o During the time that this manuscript was under its 2nd review, the FDA issued modified-exposure marketing orders to IQOS, a HTP in the US. This is based on presumably substantial evidence presented to FDA that IQOS users are exposed to lower levels of harmful constituents than are cigarette smokers. Though of course long-term clinically relevant outcomes are not known yet, the likely reduced-harm of HTPs should be mentioned in the paper (i.e. adding beyond what’s in the current manuscript which essentially says that HTP risks entirely unknown). o I am satisfied with the changes made to the abstract, as HTPs (which may be lower-risk but are certainly not completely safe) go along with other risk behaviors and it does not make sense to single out HTPs for intervention efforts. I would like to see this message in the main manuscript (Discussion especially) as well.
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	o Another factor that, in my reading, lessens concern about HTPs is that use remains extremely low in this sample (3%), despite high awareness and susceptibility (both over 50%). This manuscript's stated main outcome is susceptibility, but that doesn't seem to be translating into actual use. Can the authors comment on this discrepancy, especially with respect to why use rates of under 3% of a lower-exposure tobacco product are cause for concern?
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<b>REVIEWER</b>	Ai Hori University of Tsukuba, Japan
<b>REVIEW RETURNED</b>	08-Sep-2020

<b>GENERAL COMMENTS</b>	Although the authors calculated the VIF for each variable, the concern about the adjusted odds ratio for "friend uses e-cigarettes" remained. The variable could be omitted from the model if it is not the major factor associated to the outcome. I think specialist statistical review may be a better choice.
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### VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Arielle Selya

Institution and Country: Pinney Associates, Inc., USA, Sanford Research, USA

Please state any competing interests or state 'None declared': Between my initial review and my 2nd review of this manuscript, I became employed by Pinney Associates, Inc. which provides consulting services to JUUL on tobacco harm minimization.

Please leave your comments for the authors below:

This revision addressed several of my concerns, regarding the sample and its generalizability, the more thorough description of Jessor's Problem Behavior Theory, and whether awareness of HTPs is necessary for susceptibility. The authors also made some appropriate changes relating to the possibly lower degree of risk of HTPs. I still have some remaining concerns:

- Fundamentally, this manuscript seeks to intervene on youth HTP use, based on (among other things) other, riskier behaviors (e.g. cigarette smoking, binge drinking). Considering a central premise of this manuscript that risk factors cluster together, it seems to me that HTPs don't warrant much concern for the following reasons:

o During the time that this manuscript was under its 2nd review, the FDA issued modified-exposure marketing orders to IQOS, a HTP in the US. This is based on presumably substantial evidence presented to FDA that IQOS users are exposed to lower levels of harmful constituents than are cigarette smokers. Though of course long-term clinically relevant outcomes are not known yet, the likely reduced-harm of HTPs should be mentioned in the paper (i.e. adding beyond what's in the current manuscript which essentially says that HTP risks entirely unknown).

Thank you for your comment. Our manuscript reports on tobacco products (including HTPs) and electronic cigarettes use among a population exclusively made up of adolescents living in Guatemala, which is a country with a very weak tobacco control and where all of these products are unregulated. Our manuscript refers only to perceptions and use among adolescents in this environment. Reviewing the evidence from the FDA authorization goes beyond the scope of our manuscript.

Furthermore, it is important to note the distinction between modified risk and modified exposure in the FDA order: "we deny the marketing of the modified risk tobacco products with reduced risk claims at this time, and we authorize the marketing of the modified risk tobacco products with the following reduced exposure claim...". Hence, the FDA determined that the evidence is not sufficient to conclude that HTPs reduce risk. We therefore feel uncomfortable stating that HTPs likely reduce harm and



laying out these nuances go beyond the scope of the paper.

Nevertheless, we have added the following sentence to the introduction section to inform readers of the July 7th, 2020 order:

“In July of 2020, the FDA authorized Philip Morris to make claims in its HTP (IQOS) marketing about reduced exposure to harmful constituents compared to cigarettes; however, the FDA prohibited marketing claims about reduced risks from IQOS use, citing the lack of evidence for this claim. Nevertheless, consumers equate reduced exposure with reduced risk...”

o I am satisfied with the changes made to the abstract, as HTPs (which may be lower-risk but are certainly not completely safe) go along with other risk behaviors and it does not make sense to single out HTPs for intervention efforts. I would like to see this message in the main manuscript (Discussion especially) as well.

Thank you for your comment. We have revised our Introduction and Discussion sections to better reflect the risk of tobacco products in general, including HTPs. While the FDA does state that there is sufficient evidence to support claims of reduced exposure to harmful products in HTPs versus cigarettes, we believe that as tobacco products, they should still be regulated if targeting adolescents (which is the topic of our manuscript), particularly because the risk of use is still largely unknown. However, we have removed the following from the Discussion to further state the importance of knowing who is at high risk for tobacco product use in general, rather than specifically HTP use:

“This study adds evidence to the literature to assist decision-makers in building a profile to identify the subset of adolescents who are most at risk for tobacco use (including HTPs). In addition, our findings provide evidence to support FCTC programs which could reduce current HTP use and potentially use of other tobacco products as well as deter future use among adolescents.”

o Another factor that, in my reading, lessens concern about HTPs is that use remains extremely low in this sample (3%), despite high awareness and susceptibility (both over 50%). This manuscript’s stated main outcome is susceptibility, but that doesn’t seem to be translating into actual use. Can the authors comment on this discrepancy, especially with respect to why use rates of under 3% of a lower-exposure tobacco product are cause for concern?

Thank you very much for your comment. We recognize that awareness and susceptibility might not translate into future use. Therefore, we have edited the Discussion accordingly. The sentence below has been removed:

“This phenomenon could be seen across the world, where there may be a rapid increase in consumption as availability grows.”

In addition, the following has been edited in the Discussion. It now reads:

“Despite its limitations, this study is the first of its kind to examine HTP use and its correlates among adolescents in an LMIC. While current HTP use was low in our study, awareness and susceptibility were high and therefore use of IQOS and other HTP products might increase as they become more widely available.”

Reviewer: 2

Reviewer Name: Ai Hori

Institution and Country: University of Tsukuba, Japan

Please state any competing interests or state ‘None declared’: None declared.

Please leave your comments for the authors below:

Although the authors calculated the VIF for each variable, the concern about the adjusted odds ratio for “friend uses e-cigarettes” remained. The variable could be omitted from the model if it is not the major factor associated to the outcome. I think specialist statistical review may be a better choice. Thanks for your comment. We re-ran the full models after removing the “friend uses e-cigarettes” variable and compared results with the original model. There are minimal differences in the

coefficients across models, and the direction, significance, and interpretation are the same across model specifications. Because of the importance of peer influence for youth tobacco use, we keep the model as specified in the original analysis. For simplicity, we have not included the tables from the sensitivity analysis, but we will make them available upon request.

We now mention the adjusted model without friend use of e-cigarettes as a sensitivity analysis in the manuscript in the Statistical Analysis section of the Methods.

“Also, due to concern regarding the strong influence of friend use of e-cigarettes, we re-ran the full models after removing this variable and compared results with the original model. There were minimal differences in the coefficients across models, and the direction, statistical significance, and interpretation are the same across model specifications. Because of the importance of peer influence for youth tobacco use, we report on the results from the original model that includes the friend use of e-cigarettes variable.”

### VERSION 3 – REVIEW

<b>REVIEWER</b>	Arielle Selya PinneyAssociates, Inc., USA  I am a full-time employee of PinneyAssociates, Inc., which provides consulting services on tobacco harm reduction on an exclusive basis to Juul Labs, Inc.
<b>REVIEW RETURNED</b>	16-Nov-2020
<b>GENERAL COMMENTS</b>	The authors have addressed all of my concerns.