What is the impact of vaping on smoking, nicotine intake and toxin exposure among youth in England compared with youth in North America?

Protocol for the NIHR study (Version 2)

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1.0 Introduction

Growing concerns have been raised with respect to vaping among youth, with substantial increases observed in recent years within Canada and the United States (Cole, Aleyan, Battista, & Leatherdale, 2020; Hammond et al., 2019). Within England, vaping experimentation has increased, whereas regular use has remained fairly stable over time (McNeill et al., 2019). It remains unclear what may be driving these cross-country differences; however, it may be due to differences in e-cigarette regulatory frameworks. For instance, within the United Kingdom, there are limits set on the nicotine concentration present within e-cigarettes (20 mg) and marketing of e-cigarettes is restricted to local channels (e.g., billboards, posters) (UK Government, 2016). In contrast, within Canada, e-cigarette marketing is permitted through mass media channels, such as radio, television and print providing the content of advertisements do not appeal to youth or include lifestyle advertising (Health Canada, 2018). Furthermore, the maximum nicotine content permitted in e-cigarettes is 66 mg/ml (Health Canada, 2018). In the United States (US), there are few federal restrictions on e-cigarette marketing and there are no limits on the amount of nicotine permitted in e-cigarettes (Sharpless, 2019).

Concerns about youth exposure to nicotine from vaping have also increased in light of the advent of nicotine salt technology that enables the delivery of higher concentrations of nicotine. In contrast to free-base nicotine, nicotine salt products facilitate the delivery of higher concentrations of nicotine while reducing the nicotine impact on the upper airways (Talih et al., 2019) and are designed to improve the sensory experience of e-cigarette use. This may be important for new e-cigarette users and may have played a role in the popularity of e-cigarette use among young people, including those who have never smoked. Other health concerns include the outbreak of acute lung diseases (E-cigarette, or Vaping product use Associated Lung Injury (EVALI)) that occurred in 2019, mostly in the US. The US Centers for Disease Control and Prevention (CDC) have attributed vitamin E acetate-contaminated tetrahydrocannabinol (THC)-vaping products (vitamin E acetate is used to thicken THC oils) as the culprit in the EVALI outbreak (Centers for Disease Control and Prevention (CDC), 2020) rather than nicotine vaping products. Given the popularity of e-cigarettes as a drug delivery system, it is possible that some youth in England may be using e-cigarettes to vape illegal THC and other products. However, there have been no surveys conducted to date in England investigating the possible health effects of e-cigarette use among youth.

Concerns about the potential health effects of vaping among youth in the US have increased the urgency for research in this area. To that end, biomarker studies provide an opportunity to generate timely evidence enabling the examination of potential health risks of e-cigarette use among youth. Additionally, international studies that facilitate comparisons across countries with divergent e-cigarette regulatory environments may provide a deeper understanding of what may be driving differences in rates of e-cigarette use in England versus Canada/the US.

2.0 Study Aims

The current study extends an existing **international survey (the ITC Youth Tobacco and Vaping Surveys) and associated Biomarker Sub-Study** led by Prof. David Hammond from the University of Waterloo to answer important questions about the impact of English vaping policies on vaping and its health consequences among a sample of youth.

Aims for NIHR study: To compare vaping and smoking patterns and toxicant and nicotine exposure, and respiratory symptoms among youth (16-19 years old) who vape with youth who smoke, vape and smoke, and youth who do neither, in England, compared with youth in Canada and the US that have different e-cigarette regulations.

Research Questions for NIHR study:

1. How do patterns of vaping and smoking among youth in England compare with patterns in Canada and the US, which have different e-cigarette regulations?
2. How does exposure to potential toxicants and nicotine differ between *youth vapers, smokers, dual users and non-users*, in England compared with Canada and the US?
3. How does exposure to potential toxicants and nicotine differ between *youth vapers of nicotine salt products* in England compared with Canada and the US?
4. What is the association between e-cigarette use and reported respiratory symptoms among youth in the three countries?

We will conduct patient and public involvement with young people to inform research and dissemination.

2.1 Outcomes/Endpoints

ITC Youth Tobacco and Vaping surveys
Primary: smoking and vaping status, including frequency of smoking and vaping between England and US/Canada.
Secondary:

- respiratory symptoms reported by past-week vapers, smokers, dual users and non-users
- e-cigarette type/product(s), brand(s) and flavours used
- use of vaping products with nicotine (including nicotine content and nicotine salts)
- measures of nicotine dependence
- differences in susceptibility measures for smoking and vaping among non-users between England and Canada/US

Biomarker sub-study
Primary: a comparison of the four different types of biomarker data (nicotine metabolites, the tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), volatile organic compounds (VOCs), Polycyclic aromatic hydrocarbons (PAHs), across past-week vapers, past-week dual users, past-week smokers and non-users (of tobacco, vaping products, or cannabis in the past 30 days) between England and Canada/US.
Secondary: biomarker differences between nicotine salt e-cigarette users in England compared to Canada/US.

3.0 Study Methodology

3.1 ITC Youth Tobacco and Vaping Survey

The ITC Youth Tobacco and Vaping Survey is an online survey that was designed to examine the uptake of nicotine vaping products (NVPs) among youth in three countries with different policy environments: the United States (US), Canada and England (Hammond et al., 2019; Hammond, Reid, & Boudreau, 2020; Hammond, Reid, Rynard, & Burkhalter, 2020; Hammond, Reid, White, & Boudeau, 2018). The ITC Youth Tobacco and Vaping Survey included questions on the use of e-cigarettes (all models) and tobacco use (including manufactured and rolling tobacco). Questions also included self-reported dependence to various products (e.g. by asking participants 'do you consider yourself addicted to cigarettes/e-cigarettes', urges to use the product and measuring self-reported frequency of smoking, vaping and dual use).

The ITC Youth Tobacco and Vaping Surveys were initially administered annually during the first three waves of the study (W_1: 2017, W_2: 2018, W_3: 2019), and were originally funded by US NIH. However, in light of recent increases in youth e-cigarette use observed in Canada (Cole, Aleyan, Battista, & Leatherdale, 2020; Hammond et al., 2019), the ITC Youth Tobacco and Vaping Surveys were enhanced with funding from Health Canada to include additional half-yearly surveys (2020a, 2021a, with the original surveys becoming 2020b and 2021b) and four-week follow-up surveys. The additional half-yearly surveys and four-week follow-up surveys were added to enable more rapid and detailed assessment of vaping patterns among youth in Canada, the US and England. The four-week follow-up survey was also designed to examine patterns of smoking and vaping use and dependence in more depth, including transitions to more frequent vaping use and the potential emergence of nicotine dependence among youth. Technical reports are available at http://davidhammond.ca/projects/e-cigarettes/itc-youth-tobacco-ecig/

3.1.1 Eligibility Criteria

Inclusion Criteria

Eligible respondents for ITC Youth Tobacco and Vaping Surveys include youth aged 16-19 from Canada, England and the US at the time of recruitment. Initially the recruitment criteria only included youth aged 16-19 but were to be extended to include 20-29 year olds for the 2020b wave only.

Exclusion Criteria

No exclusion criteria exist, except age (as described above) and not residing in England, Canada, or the US (residents of the territories were excluded in Canada).

3.1.2 Recruitment Procedures

The sample is recruited from the Nielsen Consumer Insights Global Panel, which maintains panels in the Canada, England and the US. The Nielsen panel is recruited using both probability and non-probability sampling methods in each country (Czoli, Goniewicz, Palumbo, White, & Hammond, 2018).

Respondents are recruited either directly or through their parents. Email invitations are sent to a sample of panellists that met the eligibility criteria. Panellists who were known to be parents were also contacted. Parents who confirm they had one or more children aged 16-19 living in their household were also contacted.

3.1.3 Consent Procedures

After screening participants for eligibility, all potential respondents are provided with information about the study; specifically, an onscreen information letter is provided in the online survey. This page is shown to all potential respondents when they first log into the survey. The survey explicitly asks respondents to indicate whether they consented to participate in the study.

Participants have the option to withdraw their participation in the study at any time by not submitting their responses to the survey questions (i.e., not clicking 'next' to advance to the next question or to the end screen, or closing the browser window before completing the survey).

3.1.4 Participant Remuneration

Respondents receive remuneration in accordance with their panel's usual incentive structure, which could either include monetary awards or points-based rewards and/or chances to win monthly prizes.

3.1.5 Study Setting

These are completed online by participants in Canada, England and the US.

3.2 Biomarker Sub-Study

The funding obtained from Health Canada (described in Section 3.1) has been used to establish the biomarker sub-study. Briefly, this sub-study involves participants completing a short questionnaire and providing a urine sample. The biomarker sub-study aims to examine biomarkers of exposure to vaping products and cigarette smoking among young people, including associations with frequency of use and types of vaping product(s) used.

3.2.1 Eligibility Criteria

Inclusion Criteria

Eligible respondents include youth aged 16-19 from Canada, England and the US at the time of recruitment who were current participants of the ITC Youth Tobacco and Vaping survey described above (Refer to Section 3.1) and who belonged to a panel that allowed researchers to approach respondents for inclusion. They also need to pass the data quality question in the ITC Youth Tobacco and Vaping survey (i.e., asking respondents what the current month was), have parental permission to participate if under 18, and be living at an address where they would be able to receive mail for at least the next four weeks and provide their contact information including postal address. They had to be in one of four groups:

1) Past week vapers only
2) Past week smokers only
3) Dual users (past week smokers and vapers)
4) Non-users (no tobacco or vaping product or cannabis use in the last 30 days)

Exclusion Criteria

No exclusion criteria exist, except age and participation in the ITC Youth Tobacco and Vaping survey, as described above and their responses placing them in one of the four eligible groups.

3.2.2 Recruitment Procedures

The sample for the biomarker sub-study is recruited from our existing sample of youth participating in the ITC Youth Tobacco and Vaping survey. At the end of the survey, respondents that are part of a panel that allowed participant contact and are also eligible and interested in participating in the biomarker sub-study are told that they may be selected for this additional study. Among those who are selected to participate in the biomarker sub-study, an email is sent to confirm they are still interested in participating in the study before a kit is sent.

3.2.3 Consent Procedures

At the end of the ITC Youth Tobacco and Vaping survey, participants are provided with information about the biomarker sub-study and what is involved in participation. Participants are then asked to provide their consent to participate in the biomarker sub-study. Those who are under the age of 18 are asked to have their parent/legal guardian consent to their participation in the biomarker sub-study. Those who consent to participating in the biomarker sub-study are sent a short questionnaire, a urine collection kit, instructions and shipping materials.

3.2.4 Data Collection

Short Questionnaire

Participants in the biomarker sub-study are asked to complete a short pen and paper questionnaire designed to collect data on past-week e-cigarette use, tobacco use and cannabis use, at the time of their bio-sample collection. Measures are also included to examine last e-cigarette used, including flavours used, nicotine concentrations, brand and nicotine salt or non-salt e-liquid.

Bio-Sample Collection

Participants are advised to collect their urine sample as soon as possible (ideally within the next 5 days). Participants are provided with ‘what to do’ instruction sheets to guide them on how to collect their urine sample, pack the sample and post the sample and short questionnaire. Shipping materials are pre-labelled with unique numeric ID labels to ensure unique participants can be identified while preserving anonymity during transit and storage.

3.2.5 Bio-Sample Procedures

Bio-Sample Shipping & Storage

After study participants from England have collected a urine sample, the kit and questionnaire are sent to King’s College London using postage paid envelopes, in order to ensure no personal information is linked to participants and that the anonymity of participants is maintained. Once the samples are received by King’s College London’s research facilities, the genetic material is removed from the urine samples by centrifuge within seven days of receipt. The samples are then stored in a -20 degree Celsius freezer until all the samples have been collected. Once the collection of all samples is complete, the samples are sent to the Roswell Park Comprehensive Cancer Centre in Buffalo, New York, US.

For participants in the US the kit and questionnaire are sent directly to Roswell Park Comprehensive Cancer Centre in Buffalo. For participants in Canada, the kit and questionnaire are sent to the University of Waterloo for processing before being sent to Roswell Park Comprehensive Cancer Centre in Buffalo once collection was complete.

Sample Analysis

At Roswell Park Comprehensive Cancer Centre, the samples will be analysed to provide estimates of exposure to potentially harmful constituents across the four user groups (past week vapers, past week smokers, past week dual users, and non-users) in all three countries. Urine samples will be tested using highly selective mass spectrometric methods (Goniewicz et al., 2018; Shahab et al., 2017) for: a) nicotine metabolites (including cotinine and hydro cotinine); (b) NNAL which is a metabolite of the tobacco-specific nitrosamine NNK; (c) Volatile Organic Compounds which test exposure to numerous toxic chemicals present in smoke, and in small quantities in vaporised products (including acrolein, acrylonitrile, acrylamide, and benzene metabolites); (d) Polycyclic aromatic hydrocarbons (PAHs), which are a toxic by-product of combustion and enable identification of any combustion occurring in the products; and (e) Creatinine, for correction.

All sample testing will be undertaken at Roswell Park Comprehensive Cancer Centre, to ensure comparability across countries. Analysing samples at different laboratories is likely to introduce laboratory specific batch effects due to the use of different sample preparation, instruments, and/or data analysis pipelines (Gika et al., 2010).

3.2.6 Participant Remuneration

Participants of the biomarker sub-study are provided with an Amazon gift card.

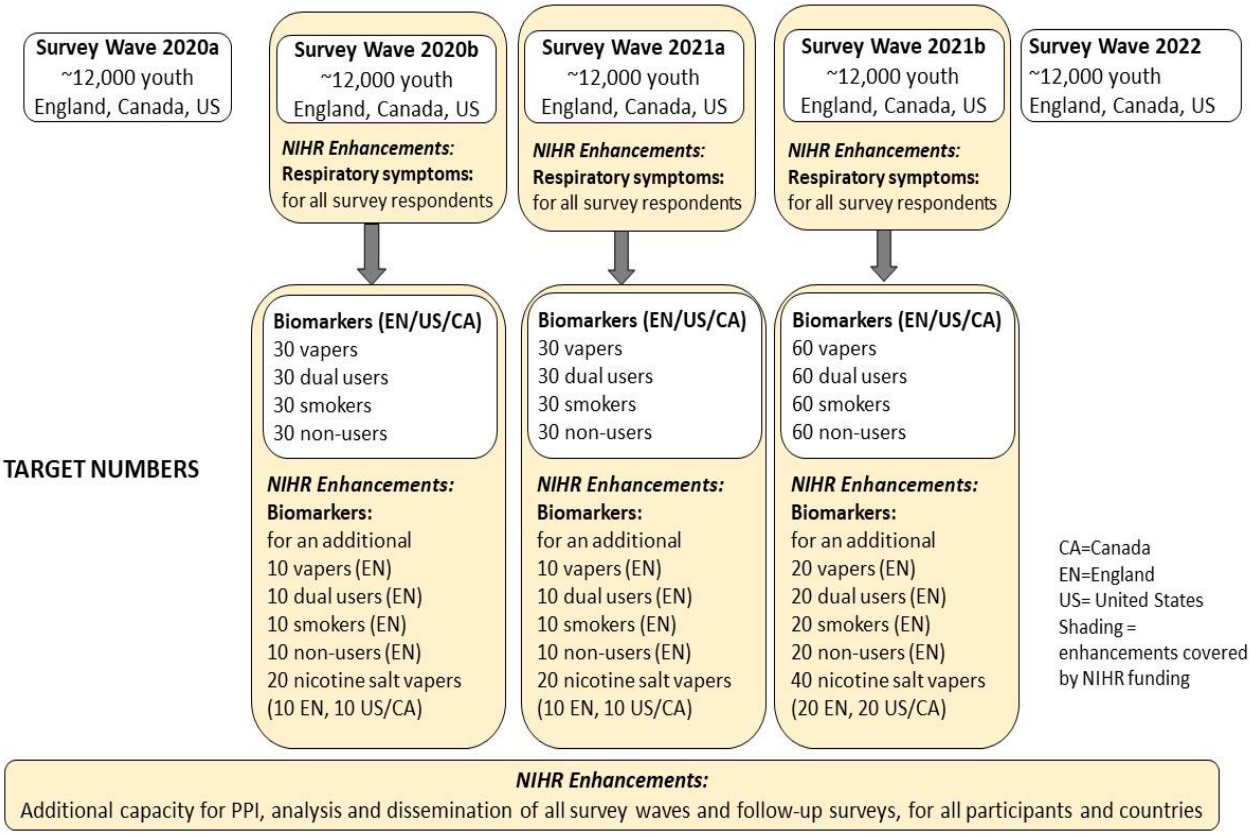
3.2.7 Study Setting

Urine kits are sent out to participants to complete at home, along with the short questionnaires that are to be completed by participants using paper and pencil. Participants in England then post their samples to King's College London to remove genetic material and for temporary storage, before they are sent in batches to the US Roswell Park Comprehensive Cancer Centre for biomarker analysis following a tested protocol (Shahab et al., 2017).

3.3 NIHR-funded Enhancements

NIHR funding is being used to enhance the above studies in several ways, including to build overall capacity in England to analyse the ITC youth survey data. An overview of the main enhancements made under the NIHR study are described in further detail below (see also yellow shading in Figure 1).

Figure 1: Study Flow Chart (Yellow shading denotes NIHR enhancements)



3.3.1 ITC Youth Tobacco and Vaping Survey enhancement

Additional questions on the presence of respiratory symptoms are added to the ITC Youth Tobacco and Vaping survey (Survey Wave 2020b onwards). Questions were adapted from the WHO Health Behaviour of School-aged children survey on asthma and wheezing (Hublet, De Bacquer, Vereecken, & Maes, 2004; Lochte, Petersen, Nielsen, Andersen, & Platts-Mills, 2018). Questions also replicated those used in a randomised controlled trial of e-cigarettes for smoking cessation (Hajek et al., 2019). These questions examine whether respondents had experienced various respiratory symptoms including shortness of breath, wheezing, chest pain, a cough and the presence of phlegm.

3.3.2 Biomarker Sub-Study enhancement

We sought to enhance the sample size of the biomarker sub-study to allow for the examination of cross-country comparisons (i.e., between England versus the United States/Canada). An overview of the recruitment targets set out for the biomarker sub-study are given in Figure 1. In summary, an additional 240 participants would be recruited to give bio-samples.

4.0 Statistical Analysis for NIHR-funded study

4.1 Biomarker Analysis

Using T-tests and one-way ANOVAs, we will *compare biomarkers of exposure to: a) nicotine metabolites (including cotinine and hydroxycotinine); b) NNAL; c) VOCs and metabolites; d) PAHs and; e) creatinine* among **past-weekly vapers** in England versus those in Canada and the US. These comparisons will also be tested on each outcome of interest described above using multivariable linear regression, adjusting for relevant sociodemographic and behavioural covariates. These covariates include indicators of socio-economic status (SES), family/friends' smoking behaviours, grilled meat consumption, smoking cannabis, smoking tobacco, vaping cannabis, other tobacco use and the use of nicotine replacement therapy (NRT).

Similar analyses will be conducted to compare *biomarkers of exposure* among (i) **past-weekly dual users;** (ii) **past-weekly smokers;** ;(iii) **non-users**; and (iv) **nicotine salt vapers,** in England versus Canada/US.

4.2 Support for Analysis of ITC Youth Tobacco and Vaping Survey Data

Using multivariable logistic regression, we will examine differences in *frequency of smoking and vaping* among youth in England versus those in Canada/US. Logistic regression models will adjust for relevant covariates including age, sex, race/ethnicity, indicators of SES and tobacco/cannabis use.

Using multivariable logistic regression, we will compare how the *type of e-cigarette product used, use with nicotine, nicotine content, e-cigarette brand, use of nicotine salts and measures of nicotine dependence* differ among vapers in England versus vapers in Canada/US. Logistic regression models will adjust for relevant covariates including age, sex, race/ethnicity and indicators of SES.

Using multivariable logistic regression, we will compare differences in *measures of susceptibility* among non-vapers/non-smokers in England compared to non-vapers/non-smokers in Canada/US. Logistic regression models will adjust for relevant covariates including age, sex, race/ethnicity, SES indicators, tobacco/cannabis use, alcohol use, and family/friends' use.

4.2.1 Analysis of Respiratory Symptoms Data

Primary Comparison

Using bivariate logistic regression, we will compare *the prevalence of respiratory symptoms including a) shortness of breath; b) wheezing; c) cough and; d) phlegm* among **past-weekly vapers** in England versus those in Canada/US. Group comparisons will also be conducted on each outcome of interest described above using multivariable logistic regression models adjusting for relevant covariates. Analyses will include self-reported COVID-19 symptoms, symptoms of asthma and information on past smoking and vaping behaviour.

Similarly, bivariate and multivariable logistic regression will be used to compare the *prevalence of respiratory symptoms* among (i) **past-weekly dual users;** (ii) **past-weekly smokers;** and (iii) **non-users** in England versus Canada/US.

Secondary Comparison

Using bivariate logistic regression, we will compare *the prevalence of respiratory symptoms including a) shortness of breath; b) wheezing; c) cough and; d) phlegm* among exclusive vapers versus exclusive smokers. These comparisons will also be tested on each outcome of interest using multivariable logistic regression models, adjusting for relevant covariates. Analyses will include self-reported COVID-19 symptoms, symptoms of asthma and information on past smoking and vaping behaviour.

Similarly, bivariate and multivariable logistic regression models will be used to compare the prevalence of respiratory symptoms among (i) vapers versus dual users (i.e., smokers and vapers); (ii) vapers versus non-smokers/non-vapers; and (iv) nicotine salt vapers in England versus Canada/US.

4.3 Power Calculations

4.3.1 ITC Youth Tobacco and Vaping Survey

For the youth survey, power calculations were conducted to determine whether we would have sufficient power to detect differences between countries. These calculations indicated we had sufficient power to detect a difference of approximately 1.0% between countries in any given year (for a 2-tailed test, where alpha= 0.05 and power= 0.8). This was specifically based on sample sizes of 4,000 respondents per country and England's prevalence of vaping 20+ days per year from our 2018 ITC Tobacco and Vaping Youth Survey (1.9%).

4.3.2. Biomarker Sub-study

For the biomarker study, power calculations were conducted to determine whether we would have sufficient power to detect differences between countries. Given the lack of available biomarker data for the age group examined in this sub-study, it is more difficult to estimate power calculations for biomarkers of exposure. An example of a sample size calculation based on one biomarker, 3-hydroxypropyl mercapturic acid (3-HPMA), is presented. Specifically, the power calculation for one-way ANOVA tests demonstrated that N=40 per country group was sufficient to detect overall differences of an effect size of around 0.32 (Cohen Medium effect size) in 3-HPMA, where alpha=0.05 and power=0.8.

5.0 Data Handling & Record Keeping for all studies

5.1 Anonymization of Data

All instructions and study materials sent to participants of the biomarker sub-study/NIHR study will be pre-labelled with unique numeric ID labels in order to ensure unique participants can be identified while simultaneously preserving their anonymity during transit and storage. After participants have collected their urine sample and completed the questionnaire, the urine kits and short questionnaire will then be sent back to King's College London using prepared postage-paid envelopes in order to ensure that no personal information can be linked to the sample.

5.2 Transport and Storage of Materials

Urine samples and short questionnaires will be temporarily stored at King's College London. Afterwards, the urine samples will be transported and stored at Roswell Park Comprehensive Cancer Centre in the United States. The transfer of biological materials between the two institutions will be done in accordance with the terms of the Material Transfers Agreement agreed by both parties.

5.3 Data Access & Sharing

Only the research team will have access to the study data. For data transfers, data will be securely transferred by the University of Waterloo study personnel to the research partners at King's College London using the University of Waterloo's secure file transfer service (Sendit). This service transfers files using a secure link that is encrypted and requires a password.

6.0 Archiving for all studies

Data gathered from the urine analysis will be stored at Roswell Park Cancer Centre electronically for at least seven years after the completion of the study and all data will be anonymized. The data gathered from the ITC Youth Tobacco and Vaping Surveys will be stored electronically on a secure University of Waterloo server for a minimum of 7 years after the completion of the study and all data will be anonymized.

The urine samples will be destroyed one year after testing is conducted at Roswell Park Cancer Centre. The short questionnaires that are administered will also be destroyed once data entry is complete.

7.0 Monitoring Procedures for all studies

In light of COVID-19, ongoing monitoring of the lockdown rules within England will be undertaken. In the event that a 'stay at home' order is issued that prevents participants from being able to send their urine kit and short questionnaire back to lab by post, the study will be paused until these rules are lifted.

As this study does not provide a specific product or intervention to participants, we will not be undertaking monitoring of adverse events.

8.0 Ethical Considerations

This bio-marker sub-study involves the collection of urine samples from young people. However, ethics approval have been sought to date, and will be sought for the forthcoming data/biomarker collection, from King's College London and the University of Waterloo.

9.0 Peer Review

The NIHR study has undergone an independent peer review by five reviewers as part of the NIHR grant review process. An internal member of the team at King's College London also volunteered to review the NIHR grant prior to submission.

10.0 Patient and Public Involvement in the NIHR study

Following the pilot testing of the study procedures for the bio-sample collection, a focus group with eight participants aged 18-21 from south London was conducted to gain feedback on this study. Based on their feedback, improvements to study procedures that were suggested including emphasizing messages around confidentiality and sample collection were implemented. Similar focus groups with a local advisory group of young people will also be coordinated at the start, middle and end of the research study to inform data collection, bio-sample collection procedures and interpretation of study findings.

Formal arrangements will be established to work with an advisory group for young people-ALPHA (Advice Leading to Public Health Advancement). ALPHA is part of DECIPHer - the

Centre for the Development and Evaluation of Complex Interventions for Public Health Improvement, one of five UKCRC Public Health Research Centres of Excellence coordinated by the Medical Research Council. ALPHA includes a group of young people aged 14-22 who live in Bristol and Wales. They coordinate monthly meetings to advise researchers who want to involve youth in research. As part of their longstanding and continuous public involvement role, they have received training on and have direct experience being involved in public health research, including tobacco smoking and e-cigarette use. The ALPHA members and all sessions are supported by a dedicated Public Involvement Officer and an experienced Youth Worker. Three meetings will be arranged with ALPHA during the course of this study (dependent on COVID-19 related restrictions).

11.0 NIHR Study Committee

External oversight will be provided by a Study Steering Committee comprised of four members: Professor Linda Bauld, Professor Ed Stephens, Dr Tim Marczylo and Professor Andrea Villanti. The chosen members of the Study Steering Committee are highly qualified subject experts within the field of e-cigarette and tobacco research that hold relevant skills to act on such a committee.

12.0 Publication and Dissemination Policy for NIHR study

12.1 Publication

A minimum of four academic publications will be published in peer reviewed journals. These publications will focus on:

1. Comparisons of patterns of vaping, smoking, and dual use among youth in England, versus the US and Canada (where differing e-cigarette regulations are in effect)
2. Comparisons of biomarkers of exposure to toxicants and nicotine among youth vapers, smokers, dual users and non-users in England, versus the US and Canada
3. Comparison of biomarkers of exposure to toxicants and nicotine among youth using nicotine salt e-cigarettes in England, versus the US and Canada
4. Comparisons of respiratory symptoms among vapers, smokers, dual users and non-users

12.2 Wider Dissemination

Briefings and presentations to policy-makers will be provided in order to support evidence-based policy. Our team also works closely with colleagues at Public Health England who are responsible for Tobacco Control and e-cigarette policies. The team also has close links with the Medicine and Healthcare products Regulatory Agency (MHRA) whose responsibility includes regulation of e-cigarettes. Our team is also a member of various expert groups related to tobacco control and e-cigarette policies (e.g., NICE guidelines, NHS England). We also regularly present at the UK E-cigarette research forum, a forum for researchers, policy-makers and practitioners and are regulatory invited to present our findings at other national and international conferences and meetings, involving policy-makers and healthcare practitioners.

Members of this team are also Investigators/Co-Investigators on the International Tobacco Control Policy Evaluation Project (ITC Project) whose survey-based evidence covers over 25 countries globally. Our links with international collaborators on the ITC Project will further enable us to disseminate our results beyond England.

The study findings will also be presented at conferences during 2022-2023, including those focused on nicotine and tobacco (e.g., Society for Research on Nicotine and Tobacco international and European conferences), conferences on respiratory health (e.g., European Respiratory Society Annual Congress) and conferences focused on youth health (e.g., Association for Adolescent Health Congress, European Public Health Association).

13.0 Stop-go criteria

As we have recruited ~12,000 participants to the main surveys we do not anticipate any problems in carrying out further surveys (as above).

For the biosample component, we propose that stop/go criteria are set for 12 months following the start of this grant, when we will have run two more surveys (September/October 2020 and March/April 2021) and collected biomarker data. If the target sample of an additional 100 samples from England (20 additional past-week vapers, 20 additional dual users, 20 additional past-week smokers, 20 additional non-users, 20 nicotine salt users) plus 20 additional nicotine salt users from North America (see Table 1) has not been achieved, we will oversample the past-week vapers (rather than aim for equal numbers of dual users, a smaller category) in Spring 2021 if available to do so.

If that is unsuccessful, we have two options to continue which we will discuss with the Study Steering Committee and NIHR:

i Combine the 2020 samples with 2021 samples if the numbers of additional samples received at the time of the review are at least half the targeted numbers i.e., 50 from England and 10 nicotine salt users from North America by April 30th 2021.

ii Assess the biomarker responses from the new 20-29 year old survey and propose combining these with the 16-19 year olds.

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