Impacts of e-cigarette regulation via the EU Tobacco Products Directive on young people's use of e-cigarettes: a natural experiment

1. Background

E-cigarettes are hand-held devices which deliver smokeless nicotine through a battery-powered vaporisation process. A recent Public Health England report endorses an estimate that e-cigarettes are 95% safer than tobacco[1], although this remains contested[2 3]. Their impact for cessation has not thus far been as great as many enthusiasts had predicted, although there is growing evidence of small but significant population level impact on smoking cessation [4 5]. Hence, their harm reduction potentials have led many public health experts to urge against regulating them as tobacco products[6]. Other public health experts argue for greater regulation, pointing to emerging evidence that e-cigarettes are not adopted primarily as cessation aids[7]. Early studies indicate that most adult e-cigarette users are 'dual users', who use e-cigarettes as well as, rather than as a substitute for, tobacco [8], although more recent data show that rates of dual use in the UK are declining as a larger proportion of vapers stop smoking[9 10]. Perhaps the biggest concern among those calling for regulation is their impact on young people. While adult use has largely been limited to smokers or ex-smokers, emerging international evidence indicates increasing numbers of adolescents and young adults who have never used tobacco, are experimenting with e-cigarettes[10-12]. Concern has focused primarily on links to smoking rather than direct harms. That is, much debate has centred on whether e-cigarettes increase the likelihood that young people will take up smoking. However, some have argued that were e-cigarettes to become widely used by young people, this could in itself have detrimental public health effects[13]. Hence, governments in the UK and beyond are currently weighing up, or enacting, various regulatory responses to e-cigarettes, motivated by a desire to prevent regrowth in youth smoking and/or prevent use of e-cigarettes themselves.

On 20 May 2016, e-cigarettes were regulated under the EU Tobacco Products Directive (TPD) throughout the UK, which includes a number of components intended to limit appeal and use of e-cigarettes among non-smokers such as young people. These include a ban on cross-border advertising (i.e. TV, radio, print and some forms of online marketing), in line with concerns that e-cigarette advertising was beginning to closely mirror tobacco advertising [14], targeting non-smokers and young people[15]. Secondly, in line with data from the tobacco control literature, showing effects of large, prominent health warnings on risk perceptions among young people and non-smoking adults, e-cigarette manufacturers are expected to include a health warning covering at least 30% of the front and back of their packet. Thirdly, the TPD introduced regulation of high strength nicotine products, and mandatory child-proof packaging. A key justification for regulation, stated within the TPD is that e-cigarettes "can develop into a gateway to nicotine addiction and ultimately traditional tobacco consumption, as they mimic and normalize the action of smoking"[16]. Hence this move is premised on assumptions that e-cigarettes renormalise tobacco, and that limiting the appeal of e-cigarettes will limit the risk of an increase in smoking uptake. This has of course been opposed by the vaping community who argue both that there is no evidence that e-cigarettes renormalize smoking, and that strong regulation will limit the appeal of e-cigarettes to smokers. Some research suggests young people support regulation of e-cigarettes until harms are understood[17].

Following the recent Brexit vote, the UK may leave the EU during the period of this study. However, having already been adopted in the UK, the legislation is unlikely to be affected by this until beyond the period of the study. The Department of Health have committed to reviewing the legislation beyond this period. Below, we first discuss the evidence surrounding trends in e-cigarettes use among young people, and potential direct and indirect harms, before discussing contemporary regulatory options in the UK and beyond. We then describe the methodology for a natural experiment with embedded process evaluation to understand impacts of e-cigarette regulation via the TPD on young people's vaping in England, Scotland and Wales.

Young people's e-cigarette use; a public health issue?

Although it is unlikely e-cigarettes come close to the harms of tobacco, if widespread regular use of nicotine were to occur via e-cigarettes, this has the potential to become a public health problem. While challenging to investigate in humans, since cohort studies have been unable to isolate nicotine use from other chemicals within tobacco, evidence from animal models suggests that nicotine use during adolescence can inhibit brain development, with potential implications for later emotional and cognitive functions[18]. Some have argued that potential effects on young people's brain development have been absent from debates surrounding youth e-cigarette use, which have almost exclusively focused on hypothetical links to tobacco[13]. Studies of adolescent smokers also suggest that nicotine dependence develops relatively quickly after initiation. [19 20] New generation e-cigarettes have evolved to be more efficient and nicotine delivery from some devices may approach or even exceed that of a conventional cigarette [21 22]. As described above, in the early years of the proliferation of e-cigarettes, there was rapid growth in experimentation among young people. However, surveys of 11-16 year olds across the UK countries have found less evidence of regular use. In Wales, by 2013, experimentation with e-cigarettes reached the same level as experimentation with tobacco; both at 12%. This was not accompanied by widespread regular use; only 1% of young people had used an e-cigarette in the past month[23]. SALSUS data collected at the same time in Scotland indicated that ever use of e-cigarettes in Scotland still lagged substantially behind tobacco, with 17% of 15 year olds having tried an e-cigarette, compared to 34% having tried tobacco, though again with few regular users[24]. In England, data collected in 2014 indicated that experimentation with e-cigarettes had grown to 22% of 11-16 year olds, marginally overtaking experimentation with smoking at 18%, but regular use remained low, at 1%[25]. A smaller (N approx. 2000 per year) YouGov survey throughout Great Britain conducted in 2013 and again in 2014 yielded lower estimates of ever use, though demonstrated growth between years, from 5% to 8%, also showing that the percentage of young people believing e-cigarettes to be synonymous with tobacco in their harms had widened[26].

The latest available data from our School Health Research Network (SHRN) survey in Wales indicate that experimentation with, and regular use of e-cigarettes have grown rapidly in the past two years[27]. Overall, 18% of young people had used an e-cigarette at least once, while use of e-cigarettes at least weekly had grown to 3% in the whole sample, rising to 6% for 15 year olds. Experimentation with e-cigarettes had become almost twice as common as experimentation with tobacco. These data showed a substantial growth in "dual use" with about half of daily smokers now also reporting being regular vapers. While regular use among never smokers and non-smokers remained low, there was a substantial relative increase[23]. Rapid growth in experimentation, and the closing gap between experimentation and regular use, perhaps signal that if left unchecked, young people's use of e-cigarettes may become a public health issue, regardless of links to smoking. Hence, it is important to understand how this upward trajectory might be interrupted.

E-cigarettes as a route into tobacco use?

Evidence regarding effects of e-cigarettes on youth smoking is hotly debated. Some have argued that visibility of e-cigarettes in places where marketing or use of tobacco has been banned, may reverse public health successes in de-normalising smoking[28]. Normalisation, as a sociological concept, originates from efforts in the 1950s to create 'normal' living conditions for people with learning difficulties, enabling them to be "normalised" into mainstream society[29]. Alcohol represents a modern day example of a substance use behaviour which remains highly normalised[30]; it is used throughout the socioeconomic distribution[31] and is widely viewed as a normal part of everyday life[32]. Smoking was a majority behaviour among men for several decades in the UK, although not amongst women, and became normalised insofar as it was adopted widely throughout the socioeconomic distribution, and those who didn't smoke were tolerant and accepting of the behaviours of those who did [33]. Hence, smoking was accommodated by wider society into the interactions and institutions of everyday life. Much success in reducing smoking has been achieved through systematically reversing the normalisation of smoking[34]. Smokers are increasingly excluded from aspects of everyday life, via moves such as banning smoking in public places, with progressive legislative restriction of when and where people can smoke. This has produced, and in turn

reflected, a cultural context in which the growing non-smoking majority collectively stigmatises smoking behaviour[35-37]. While controversial, in that it has been least effective in reducing smoking among poorer groups thus generating widespread inequalities[38], diminishing social acceptance of smoking has been a powerful driver of motivations to quit smoking in adults[39] and a key factor in declining smoking uptake in youth[40]. The 'renormalisation' hypothesis suggests that the growing prevalence of smoke-like vapour from e-cigarettes will ultimately lead to a regrowth in smoking rates through increasing the extent to which smoking is seen as a "normal" behaviour, accepted and accommodated by the non-smoking majority. Were this to occur, this increased general social acceptance of smoking may in turn increase experimentation and initiation of smoking among youth.

There are, however, few parallel examples whereby the growth of one behaviour has been shown to give rise to the normalisation of a similar but distinct behaviour. Indeed, some argue that e-cigarettes may actually play an important role in de-normalising smoking[1], through social display of an alternative. Furthermore, some argue that rather than acting as a "gateway", e-cigarettes may be diverting some young people who would otherwise have become smokers away from tobacco use. To date, one small study following 16 young people in the USA who reported that they had ever used an e-cigarette, but reported no intention to smoke, found that within one year, five people had gone on to try at least one puff of a cigarette[41 42]. Our data from Wales indicated that 10-11 year olds who have tried an e-cigarette are more likely to say that they "might" smoke within two years[43]. However, evidence from the UK and the US indicates that youth tobacco use has continued to decline as experimentation with e-cigarettes has gathered pace. In a recent CDC report, smoking among teens fell below 10% for the first time, though this was largely ignored under a headline suggesting that this was "cancelled out" by growth in use of e-cigarettes [44]. Our 2013 data from Wales showed similarly that while experimentation with e-cigarettes was increasing, use of tobacco was continuing to fall. Indeed, our most recent 2015 data also provides no evidence that tobacco use has grown in line with rapid rise in e-cigarette use, with ever smoking at an all-time low. Hence, thus far, there is little evidence that the growing presence of e-cigarettes has had any impact on the secular decline in tobacco use, in terms of either renormalizing or displacing tobacco use. Studies also suggest that young people do not share the assumed conflation between cigarettes and e-cigarettes by public health professionals, with the appeal of e-cigarettes related to flavourings and the novelty element [45 46]. There remains a need however to continue to monitor e-cigarette and tobacco use rates, and particularly any impact on smoking figures were more regular e-cigarette use to gain traction among non-smoking young people. Given that as described, the renormalisation hypothesis has been a key driver of legislative decisions, such as TPD regulation, generating robust evidence for the theoretical underpinning of such intervention is vital.

Legislative responses to youth e-cigarette use

Conflicting hypotheses regarding the potential harms and benefits of e-cigarettes have led to significantly divergent international policy responses. E-cigarettes are widely available in countries such as the UK, but illegal in more than 50 countries. In Australia, prohibition has perhaps slowed their proliferation, though adult use is growing rapidly nevertheless, with a ten-fold increase in use among adult smokers in Australia between 2010 and 2013[47]. At present, most data on youth use come from European countries or the US, which have relatively liberal regulatory regimes and there are few youth data from countries with strong regulation. However, 2013 data from Canada (where only nicotine free e-cigarettes may be sold without a medicinal license, and as yet no licensed products exist) indicate that among 15-19 year olds, 20% had tried an e-cigarette and 2.6% had used an e-cigarette in the past month. One in 4 users reported that their e-cigarettes contained nicotine, with a further 20% unsure[48]. Hence, in countries with strong regulation, the emergence of e-cigarettes lags behind countries with weaker regulation, but continues to gain traction.

In many countries such as the UK, where e-cigarette use has until now been largely unregulated, there is nevertheless broad agreement that young people's use should be prevented; age of sale restrictions have passed into law in all UK countries with relative ease. However, evidence from the US suggests that in states which introduced age of sale restrictions, the downward decline in tobacco use was temporarily interrupted. Use remained stable in states which introduced legislation

and fell in those which did not[49]. Hence, even for relatively politically uncontroversial legislation such as this, debate is ongoing regarding potential unintended consequences.

In the UK, perhaps the most controversial legislative proposal to date was the Welsh Government's proposal in 2015 to ban vaping in all public places, with the then Health Minister Mark Drakeford stating in unequivocal terms that it will "prevent the renormalisation of smoking" [50]. The inclusion of this legislation within the Public Health Bill proved so controversial that it became the first Welsh Government bill to fall at Stage 4 of the legislative process. Had this passed, it would probably have represented the biggest divergence in e-cigarette regulation between UK countries. However, following the May 2016 Assembly elections, Plaid Cymru secured agreement, in exchange for their support for a Labour minority government that the Public Health Bill would only be brought back with the controversial e-cigarette elements removed. Hence, it is unlikely that this proposal will return in the short term.

From May 2016, EU legislation has brought e-cigarettes into line with the Tobacco Products Directive (TPD). Within this, cross-border advertising of e-cigarettes is prohibited, including TV and radio advertising. Scotland has legislated to go marginally further, also banning billboard advertising. E-cigarettes (other than those licensed as medicines) will be required to carry a health warning covering 30% of their packs, indicating that 'this product contains nicotine which is a highly addictive substance' on front and back of pack. Products will also be expected to include a list of ingredients, and to be sold in tamper proof containers. A maximum nicotine strength of 20ng/ml will be set. This legislation will take some time to fully bed in; products which are not TPD compliant can still be released onto the UK market until November 20th 2016, while non-compliant products can be sold to consumers until May 20th 2017. Hence, for the initial 12 month "transitional period", regulated and unregulated products will be sold simultaneously.

Theory and legislative responses: what do we know about young people's e-cigarette use?
The controversial nature of the "theory of the problem" (i.e. that e-cigarettes normalise smoking or act as a gateway into tobacco use) has been described above. However, legislative actions described above represent a range of "theories of change". Most focus on altering young people's risk of using e-cigarettes by means of addressing risk perceptions (i.e. health warnings on packets) or reducing the visibility of e-cigarettes (e.g. marketing regulation) or access to e-cigarettes (e.g. bans on sales to minors). To date, however, there is limited evidence on the extent to which e-cigarettes are viewed by young people as safe or risky products in their own right, or relative to tobacco; what limited evidence there is suggests that e-cigarettes are already viewed as highly risky by many young people[26 51 52] although there is some evidence that young e-cigarette users or those who are susceptible to e-cigarette use tend to perceive e-cigarettes as safer and healthier than cigarettes [53 54 55] including positive perceptions in relation to nicotine [56]

Recent research from the US indicates that young people's reported exposure to television advertising of e-cigarettes increased almost 3-fold from 2011 to 2013[57], while in the UK, marketing of e-cigarettes has also grown rapidly[14]. Marketing tactics closely reflect those used historically by the tobacco industry[14], and some argue that they have targeted youth[15] prompting concerns regarding exposure to pro-cigarette messages and development of positive views towards this product. Large scale survey research has indicated significant links between young people's reported exposure to advertising and their use of e-cigarettes[58], increased perceptions of safety and use in prohibited spaces [59].

While there is less research on the impact of advertising on young people in the UK, one recent study showed that young people who recalled exposure to point-of-sale displays for e-cigarettes were more likely to go on to try them[60]. There is also evidence that while exposure to all advertising media increases the odds of experimentation with e-cigarette use, this association is strongest for exposure to internet marketing for e-cigarettes[61]. There is a clear need for research to understand how the complex suite of regulation brought in via the TPD impacts young people's perceptions of, access to, and use of e-cigarettes.

2. Why is this research needed now?

As described above, the nature of young people's interactions with e-cigarettes is rapidly evolving. Hence there is an urgent need for research to monitor longer-term trends, and to understand how best to prevent non-smokers from becoming regular e-cigarette users, while avoiding limiting appeal to smokers. The international policy responses described above have been largely formed in an evidence vacuum, and driven by competing assumptions regarding the harms and benefits of e-cigarettes. Our study will primarily use routinely collected quantitative data to examine effects of e-cigarette regulation on the prevalence of young people's vaping. In addition, we will seek to qualitatively understand how young people's perceptions of e-cigarettes and their association to tobacco alter over time as the TPD moves toward full implementation. There is no possibility of pre-legislation qualitative data given that the TPD came into effect in May 2016. We will, however, be able to look retrospectively at existing survey data as well as prospectively at future data to shed light on trends pre- and post-TPD. In addition, importantly, regulation is being introduced gradually, with an expectation that all products will be TPD compliant by May 2017. Thus for the first 12 months, non-TPD compliant e-cigarettes will continue to be available alongside compliant products. This will allow us to understand issues such as how the presence or absence of health warnings is interpreted by young people. The study will also establish a data infrastructure, through pooling of youth datasets across the 3 UK countries over time, to rapidly conduct natural experiments comparing the UK nations as and when divergences in e-cigarette policy emerge between the UK countries in the coming years. Within the TPD, there is a commitment that EU "member states" must monitor long-term trends in relation to e-cigarette and tobacco use among young people including any evidence that their use is a gateway to nicotine addiction and ultimately traditional tobacco consumption. While the UK may no longer be a member state on completion of this study, the study will enable the collation of estimates of vaping and smoking from UK datasets to facilitate this long-term monitoring. While TPD regulation is expected to remain unchanged during the study period, the government has committed to subsequently reviewing the regulation https://hansard.parliament.uk/lords/2016-07-04/debates/16070434000128/TobaccoAndRelatedProductsRegulations2016; this will provide vital evidence to feed into this process.

3. Research objectives

Our primary aim is to investigate the role of e-cigarette regulation via the Tobacco Products Directive in influencing trajectories in young people's use of e-cigarettes. We will address the following key research questions in relation to this aim:

i) Does increased regulation of e-cigarettes interrupt the current trajectory of young people's e-cigarette use?
ii) How do young people perceive risks and social norms surrounding e-cigarettes (and how do these change over time as products become TPD compliant):
   a. as a product in their own right?
   b. relative to tobacco?
iii) How do young people interpret and respond to the presence or absence of health warnings on e-cigarette packets?
iv) To what extent, and in what ways, do young people continue to interact with e-cigarette marketing (e.g. via online marketing) after the prohibition of cross-border advertising?

We will also examine trends in young people's smoking behaviour over time. Given that TPD regulation occurs alongside a suite of tobacco regulation, we will not be able to draw definitive conclusions regarding whether regulating e-cigarettes impacted youth smoking. However, this will allow us to test the theoretical basis for much e-cigarette regulation including that via the TPD, which centres on assumptions that e-cigarettes renormalize smoking. We will address the following questions:

i) Have trajectories in young people's ever and current smoking been significantly interrupted (positively or negatively) by growing prevalence of e-cigarettes?
ii) Does the additional regulation of tobacco and e-cigarettes brought in in May 2016 (including TPD and plain packaging) alter the rate of decline in young people's smoking?

In addition, we will explore the implementation and context of TPD regulation including:

i) To what extent is compliance with TPD in product sales achieved, and what are the barriers, facilitators and unintended consequences of implementation?
ii) To what extent, and in what ways, do variations between UK countries in e-cigarette policy emerge during the study period?
iii) What other changes to the regulatory context of tobacco and e-cigarettes occur during the study period in the UK and across individual UK countries?

4. Research design

The research will comprise a natural experiment[62] drawing upon secondary repeated cross-sectional time-series data, with a mixed method process evaluation to understand implementation of the legislation, mechanisms of impact and context [63].

5. Study population

The youth population will comprise nationally representative samples of young people within secondary schools in England, Wales and Scotland. In Scotland, the SALSUS survey includes only those young people in S2 and S4 (i.e. 13/14 year olds and 15/16 year olds), whereas in Wales and England, data are collected from all secondary school year groups (i.e. 11-16 year olds). Qualitative data will be collected from samples of young people in all 3 countries.

6. Socioeconomic position and inequalities

The applicants have a strong track record of scrutinising the equity impacts of tobacco control intervention [64-66]. Socioeconomic patterning in the uptake and use of e-cigarettes is however less clear to date. We will use measures of socioeconomic status within the surveys, including family affluence and parental education for young people, and area deprivation where available, to examine whether changes over time in smoking uptake are patterned by SES. We will also purposively sample participants from a diverse range of socioeconomic contexts for qualitative components to ensure that a diversity of backgrounds and views are represented.

7. Planned intervention

The Tobacco Products Directive comprises a number of potential "active intervention ingredients" which may influence young people's e-cigarette use. A draft logic model (which will be further refined through PPI and consultations and used to guide qualitative interview schedules), is presented below in Figure 1.

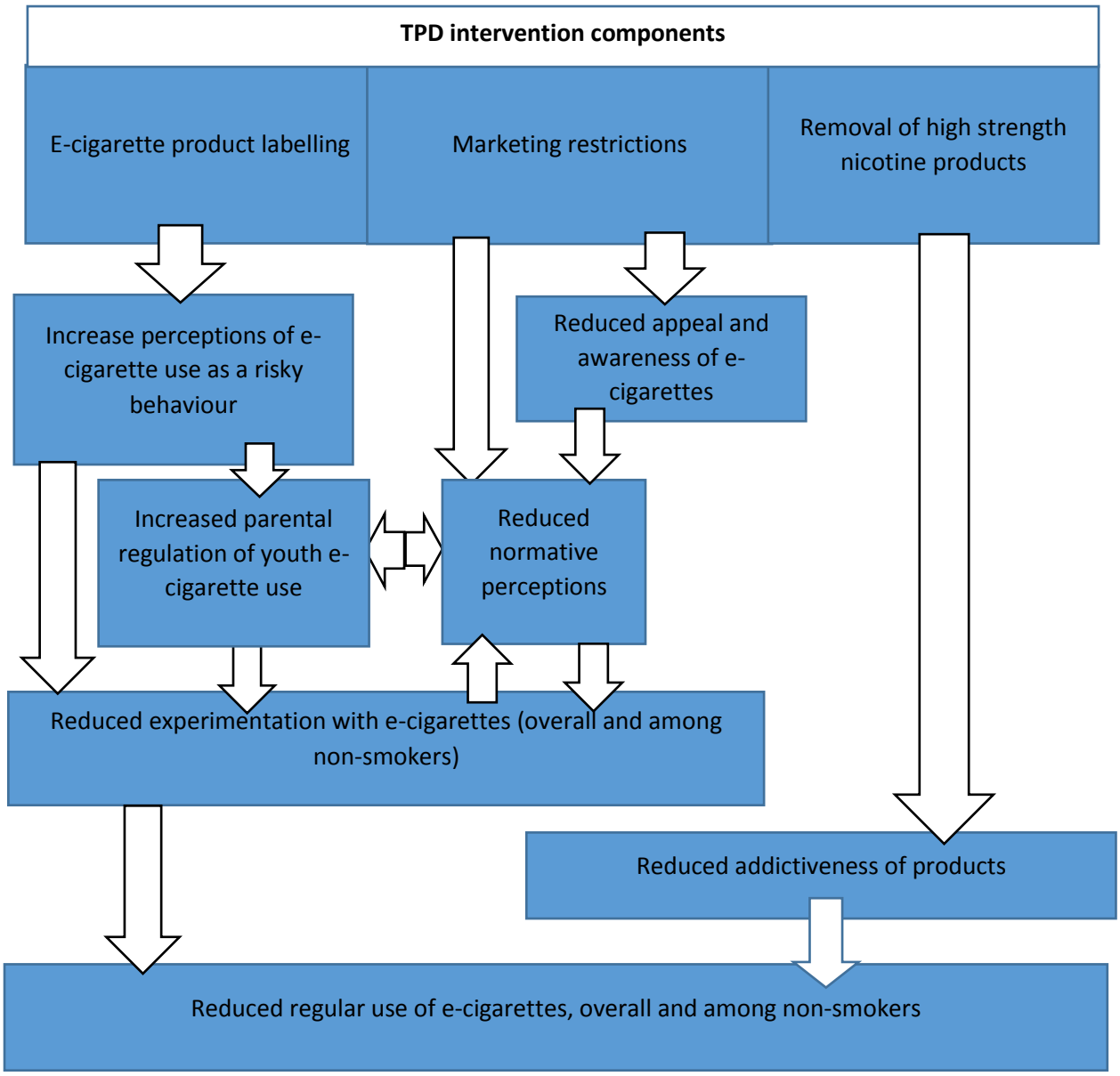
Health warnings and labelling on packets. The TPD will require non-medicinally licensed e-cigarettes to include a health warning covering 30% of their packet, if they contain nicotine. This will alert users that the device contains nicotine, which is addictive.

Evidence from tobacco control shows that prominent health warnings are perceived by both smokers and non-smokers to influence their risk perceptions, with the size of warning often equated by youth to the size of the risk[67]. Hence, it is plausible that the introduction of similar health warnings on e-cigarette packages may increase the extent to which they are viewed as a risky product by young people. However, to date, there is limited evidence on the extent to which e-cigarettes are viewed by young people as safe or risky products in their own right, or relative to tobacco, and what evidence there is suggests that e-cigarettes are already viewed as highly risky[51 52].

Marketing restrictions. The TPD will prohibit cross-border marketing of e-cigarettes (television, radio, promotional videos). In Scotland but not elsewhere in the UK, billboards and door to door leafleting will also be banned. The main remaining form of e-cigarette marketing that will still be permitted will be at the point of sale.

Recent research from the US indicates that young people's reported exposure to television advertising for e-cigarettes increased almost 3-fold from 2011 to 2013[57], while in the UK, marketing for e-cigarettes has also grown rapidly[14]. Large scale survey research has indicated significant links between young people's reported exposure to advertising and their use of e-cigarettes [58]. Marketing tactics closely reflect those use by the tobacco industry[14], and some argue that they have targeted youth[15]. The fact that the TPD removes the main forms of existing marketing could have an impact on both youth experimentation and regular use. However, notably, this legislation will not be able to fully regulate online marketing; the form which some emerging studies indicate is most influential for young people's use of e-cigarettes[61]. Furthermore, point of sale displays, which have been associated with intention to use e-cigarettes, are not regulated [60] Hence, it is possible that the removal of other forms of marketing will lead to more concentrated efforts to target youth through remaining channels.

Figure 1. Logic model for potential effects and mechanisms of TPD e-cigarette regulation



Nicotine content restrictions The maximum nicotine concentration for non-medicinally regulated e-cigarettes will also be set at 20mg/ml; stronger e-cigarettes will need to have a medicinal license. Recent estimates suggest that approximately 10% of adult vapers use e-cigarettes above this level, although no such estimate is available for young people.

While regulation came into force from May 2016, there is a transitional phase of 12 months. Non-compliant products may still be released onto the UK market until November 20th 2016. Non-compliant old stock may still be sold to consumers until May 20th 2017. As such, compliant products will be gradually introduced, and will entirely replace non-compliant products within 12 months. Regulations related to product labelling will apply only to e-cigarettes containing nicotine. Hence, after the transitional phase, there will be an increasingly clear differentiation in labelling of nicotine containing and non-nicotine containing e-cigarettes. While up until this point, surveys have typically not differentiated between nicotine and non-nicotine containing devices, on the assumption that young people would not be able to answer such questions reliably, it may be that such regulation heightens young people's awareness of the differences between these products and diverts them toward non-nicotine containing devices (rather than reducing overall vaping rates). These changes to the regulation of e-cigarettes will be implemented alongside a wide-ranging suite of regulation for tobacco cigarettes themselves, some explicitly intended to reduce the appeal and accessibility of cigarettes to young people. For the most part, the TPD brings other EU countries regulations in line with what the UK government already does. However, the introduction of plain packaging and prohibiting sales of packs containing <20 cigarettes are significant changes to tobacco policy implemented alongside the e-cigarette legislation. Plain packaging legislation came into force on the same day as the TPD. All tobacco products manufactured after May 20th 2016 must be compliant with these regulations, although there is a one-year transitional period during which old stock that has already been manufactured can still legally be sold on the UK market.

8. Methods

Outcomes evaluation datasets

Wales We will obtain historical Welsh Health Behaviour in School-aged Children (HBSC) datasets from 1998 (when youth smoking rates reached their peak) to 2013 in Wales. All of these surveys include measures of ever smoking and current smoking, Measures of e-cigarette use were introduced in 2013. An additional survey, including measures of youth smoking and e-cigarette use replicating the HBSC survey, was collected by DECIPHer in 2015 as part of the School Health Research Network (SHRN). The next planned HBSC/SHRN survey in Wales is in 2017, and a further round of SHRN data will be collected in 2019.

As this survey is led by applicants (PI: SM), it will be possible to add questions. Online purchase has been a common means internationally of subverting legislation in countries where e-cigarettes are banned, and typically enables people to obtain less regulated devices. Little is known about the extent to which young people in the UK use online outlets to obtain e-cigarettes. Hence, for the 2017 and 2019 SHRN survey in Wales, we will include additional questions on where young people who have ever used e-cigarettes obtain(ed) them from, including self-purchase via retail and online sources, as well as proxy purchase. While we will have no pre-TPD data on on-line e-cigarettes purchasing, we will also ask young people who use e-cigarettes regularly whether they have recently altered their purchasing patterns (i.e. switched to or away from online purchase). We will also ask young people who use e-cigarettes whether the e-cigarettes they use contain nicotine.

Scotland Youth smoking rates are routinely captured within the HBSC and SALSUS surveys. However, HBSC Scotland did not include e-cigarettes in their 2013 survey, it only takes place every 4 years, and is conducted in a different season to HBSC Wales (i.e. winter rather than autumn). A measure of e-cigarette use was incorporated into SALSUS in 2013, which takes place every 2 years, in the same season as SHRN/HBSC Wales. Hence, in Scotland, we will obtain historical and future datasets for SALSUS from 1998 through to 2018 for comparison with trends in Wales. A SALSUS questionnaire was planned to take place in 2017, though postponed to 2018. Data from Scotland will therefore not be included to examine short-term impacts analyses of TPD. The 2018

SALSUS data will be integrated into long term effectiveness analysis when available. Co-investigator LM is involved in the development of the new Scottish school census which is likely to replace the 2019 SALSUS survey, and will aim to negotiate retention of key items so that these data can be used within long-term effects analyses if possible.

England The Smoking, Drinking and Drug Use (SDDU) survey was conducted annually until 2015, when there was a one-year break due to lack of funding. The 2014 survey comprised 6,174 valid responses from 200 schools. Funding is however guaranteed for 2016 and 2018 surveys, while HSCIC are hopeful of obtaining funds for a 2017 and 2019 survey. Hence, we will obtain and combine all available surveys from 1998 up to 2017/19 to examine smoking trends. Questions on e-cigarette use were first integrated into this survey in 2014.

To harmonize age ranges across surveys, our initial analyses use Year Groups 9 and 11 in Wales and England (approximately comparable to the S2/S4 groups from whom SALSUS data are collected). However, within the post-TPD SDDU survey datasets, information on year group was suppressed to protect the confidentiality of pupils who were ahead or behind their natural school year. Hence, analyses of post-TPD changes in vaping and smoking will use age (13 and 15 years) rather than Year Group (9 and 11) in England.

The 2017 SHRN survey will be in the field approximately 18 months after the inception of TPD regulation (May 2016), though only 6 months after the date for full TPD compliance (May 2017) is reached. Hence, we will track trends in e-cigarette use from first introduction of these questions in 2013 through to 2017 in the first instance. However, we will subsequently extend to track through to 2019, which would give greater statistical power, and a better estimate of longer term impacts. While the applicants have unrestricted access to SHRN, as this is managed by SM and GM within DECIPHer, SALSUS and SDDU are typically released for use via the UK data archive approximately 12 months after the completion of fieldwork. Permission has been provided by Chris Roberts (Welsh Government) for use of historical HBSC datasets.

Process evaluation

Drawing upon recent guidance for process evaluation[63], we will conduct an in-depth and largely qualitative process evaluation focused on key uncertainties in the causal logic described above, in relation to implementation, mechanisms and context.

Perceptions of e-cigarettes, tobacco and TPD regulation among young people

School sampling We will recruit 12 schools overall recruited to provide i) equal representation of schools in each of the three countries; ii) an approximately equal number of high, low and medium SES schools (as indicated by free school meal entitlement) and iii) urban and rural locations. Secondly, in Wales, where data are available on school vaping rates, schools will also be sampled so as to ensure representation of schools with high and low vaping rates. Should this level of recruitment not be achieved in the first round of data collection due to the limited time between project start and full implementation of TPD, further schools will be recruited for post-legislation interviews in 2018.

Pupil sampling and data collection*.* Within each of these schools, we will conduct group based interviews, with 3-5 young people. If preferred by class teachers or young people (or where group interviews are not logistically possible) we will conduct paired interviews. We will conduct 4 group interviews (or 8 paired interviews) in each school. While smoking rates have historically been higher among girls, with convergence in genders in recent years, the opposite is true of e-cigarettes, which are becoming more popular among boys. Hence, we will conduct single sex group interviews, and will sample pupils from high and lower ability classes within secondary schools. To maximise rapport and interaction between young people within groups, we will ask school staff to identify established friendship groups. We will not explicitly attempt to recruit young people who do smoke or use e-cigarettes due to ethical challenges, and will advise teachers of this in advance of data

collection so that they do not identify groups of smokers for us. Interviews will be held on school premises, with two researchers facilitating each group interview. While it will not be possible to interview young people prior to legislation, which came into force in May 2016, it will take 12 months for all e-cigarette products to become fully TPD compliant. Hence, we will aim to interview young people as early as possible before the date of full compliance, and again one year later. Collecting data both during the transitional period and after full implementation of TPD will enable us to understand perceptions in relation to a context where unregulated e-cigarettes are, or are not, legally available for sale on the UK market.

Interview schedules Informed by our logic model (Figure 3), which we will refine in the early stages of the study through consultations with our PPI group, interviews will explore young people's perceptions of e-cigarettes, tobacco and the inter-relationship between the two, and how these perceptions are impacted by key elements of TPD regulation, such as product labelling and marketing restrictions. Interviews will also explore the broader context in which this legislation is implemented, in terms of the simultaneously introduced suite of regulation to make tobacco less appealing and accessible to young people. For example, the fact that regulation will occur alongside even further regulation of tobacco packaging may influence relative risk perceptions. It is also plausible that the regulation will not reduce overall use of e-cigarettes among young people, but that use will shift away from nicotine based and toward nicotine free devices. Interviews will also explore young people's understandings of the risks of differing types of e-cigarettes, and perceived impacts of regulation on the types of e-cigarettes used (e.g. nicotine containing or nicotine free) by themselves and peers. Given the slight differences in question wording used to measure e-cigarette use across countries, we will also explore how these survey questions are interpreted by young people, to enable better interpretation of whether differences between countries represent meaningful differences in use, or differences in interpretation of the questions asked.

Consent The consent process will comprise three stages: school-level consent for the pupils to be approached, letters for parents describing the study, with a consent form to return if they are happy for their child to participate, and finally assent from selected pupils. Schools will be asked to identify groups of pupils (aged 14/15 at baseline).

Triangulation. Our sampling methods are directed towards obtaining views from a diverse range of subgroups, rather than representativeness. This will however enable us to qualitatively unpack key elements of the logic model in a diverse range of populations, and identify areas of consensus and disagreement in terms of the plausibility of its key propositions. For example, one of the key propositions of the model is that the labelling of e-cigarettes with health warnings will increase young people's perceptions of these as risky products. This assumes i) that young people do not currently view these as risky products and ii) that labelling is an effective means of changing these perceptions. If qualitative data in these various groups led to a conclusion of consensual view that e-cigarettes (prior to full implementation of TPD) were not viewed as risky products, and that young people are persuaded by the new labelling, this proposed mechanism would retain a higher degree of potential plausibility than if the opposite were true (i.e. pupils uniformly believed e-cigarettes were risky already) or views among young people were highly divergent. Hence, qualitative data will aim to explicitly inform interpretation of quantitative outcomes. The quantitative and qualitative data will be analysed in a sequential manner, with the qualitative data collected and analysed first, prior to analysis of quantitative data on effects of TPD. Hence, this will enable the formation of a clear picture of the mechanisms through which the legislation may have impacted young people's use of e-cigarettes, and how those mechanisms may have been potentiated or thwarted in different contexts, while avoiding post-hoc rationalisation (i.e. fishing for explanations once the quantitative outcomes are known).

Implementation, compliance and context

We will audit 10 e-cigarette retailers in each country on two occasions, to quantify the availability of TPD non-compliant products. These will be conducted at times coinciding with qualitative interviews to put in context the extent to which unregulated products remain available during initial interviews

conducted during the transitional phase, where non-compliant products can still legally be sold, and whether full compliance is achieved by follow-up interviews after full compliance is expected. Two observers will independently estimate what proportion of e-cigarettes on sale in each location has compliant labelling at each time-point. Locations will be sampled purposively to include large and small mixed retailers (e.g. supermarkets and newsagents), specialist e-cigarette shops and street vendors. Approximately half of these will be in the vicinity of schools sampled for qualitative interviews. We will also conduct interviews with up to 10 e-cigarette retailers in each country after the final date for full compliance. We will conduct further interviews with policymakers (up to 5 per country) and trading standards officers (up to 5 per country) in each country in order to explore barriers and facilitators to implementing the legislation; Policy representatives will be recruited through our existing links with UK governments. We will also discuss any planned changes in the tobacco control landscape with key stakeholders within and between the UK countries during the study period, including Public Health Wales, Public Health Scotland and ASH, in order to locate the change in legislation in broader tobacco control action, and understand other changes which are occurring in one or more UK countries and could influence observed trends.

9. Outcome measures

Qualitative themes

Qualitative data will investigate a range of broadly defined themes informed by the logic model (see attached file), and discussed in the context of TPD components. In interviews with young people, these will include: i) risk perceptions of e-cigarettes and tobacco, and the inter-relationship between them; ii) perceptions of parental regulation of e-cigarette and tobacco use; iii) perceived appeal and normative perceptions surrounding e-cigarette and tobacco use; iv) interactions with marketing for e-cigarettes. Interviews with retailers, policymakers and trading standards officers will investigate perceived barriers, facilitators and unintended consequences of implementation.

Quantitative outcomes

Primary outcomes. Our primary quantitative outcome will be “ever use of e-cigarettes” (see Table 1). **Secondary outcomes.** We will analyse regular (weekly) e-cigarette use, as well as ever and regular smoking as secondary outcomes. As indicated in Table 1 below, there are slight differences in the wording of questions between surveys, although it is possible to obtain comparable estimates of “ever smoking” and “current smoking” from all surveys, and “ever e-cigarette use” (from 2013 onwards) and “current e-cigarette use” (from 2015 onwards) from SALSUS, SDDU (from 2014 onwards) and SHRN/HBSC.

10. Assessment and follow-up

The quantitative aspects of this study would be a repeated cross sectional survey design, and follow up surveys will be obtained up to 2019 (approximately 2 years after full implementation of legislation).

Table 1. Youth survey measures and data sources

Outcome	Country	Data source	Questions asked	Response options	Derived variables
Ever tried smoking	Wales	SHRN	At what age did you first do the following things? (if there is something that you have never done, choose the “never” category) – smoke a cigarette (more than a puff)	Never (or a range of ages)	Never vs all others (binary)
	Scotland /England	SALSUS/ SDDU	Read the following statements and cross the box next to the one which best describes you	“I have never smoked”, “I have only ever tried smoking once” “I used to smoke sometimes but I never smoke a cigarette now”	

Current smoking	Wales	SHRN	How often do you smoke tobacco at present? Have you ever smoked regularly* (at least once a week)	"every day", "at least once a week, but not every day", "less than once a week", "I do not smoke" Yes /no	Non-smoker, occasional smoker, regular smoker (weekly or more) With potential additional category of ex-smoker in SHRN and SALSUS
	Scotland /England	SALSUS/ SDDU	Read the following statements and cross the box next to the one which best describes you	"I have never smoked", "I have only ever tried smoking once" "I used to smoke sometimes but I never smoke a cigarette now" "I sometimes smoke cigarettes now, but I don't smoke as many as one a week", "I usually smoke between 1 and 6 cigarettes a week", "I usually smoke more than 6 cigarettes a week"	
Ever tried e-cigarettes	Wales	SHRN	At what age did you first do the following things? (if there is something that you have never done, choose the "never" category) – used an e-cigarette Have you ever tried electronic cigarettes (sometimes called an e-cigarette).	Never (or a range of ages) Yes / no	Never vs all others (binary)
	Scotland /England	SALSUS/ SDDU	An electronic cigarette is a tube that can look like a normal cigarette, can have a glowing tip and puffs a vapour that looks like smoke but unlike normal cigarettes they don't burn tobacco. Now read the following statements carefully and cross the box next to the ONE that best describes you	"I have never used an e-cigarette", "I used to use e-cigarettes but don't use them anymore", "I have tried an e-cigarette once", "I have tried an e-cigarette a few times", "I use e-cigarettes sometimes, but no more than once a month", "I use e-cigarettes more than once a month but less than once a week", "I use e-cigarettes once a week or more"	Never vs all others (binary)
Regular e-cigarette use	Wales	SHRN	How often do you use e-cigarettes at present?* Have you ever used e-cigarettes regularly? (at least once a week)	"every day", "at least once a week, but not every day", "less than once a week", "I do not use e-cigarettes at present" Yes/No	Non-user, occasional user (i.e. less than weekly), regular user (weekly or more). Potential additional category of former user
	Scotland /England	SALSUS/ SDDU	An electronic cigarette is a tube that can look like a normal cigarette, can have a glowing tip and puffs a vapour that looks like smoke but unlike normal cigarettes they don't burn	"I have never used an e-cigarette", "I used to use e-cigarettes but don't use them anymore", "I have tried an e-cigarette once", "I have tried an e-cigarette a few times", "I use e-cigarettes sometimes, but no more than once a month", "I use e-	

			tobacco. Now read the following statements carefully and cross the box next to the ONE that best describes you	cigarettes more than once a month but less than once a week", "I use e-cigarettes once a week or more"	
*Included from 2015					

* At the time of writing, there is no confirmed funding for a 2017 SDDU survey, though the organisers are seeking funding in the hope that it will go ahead. If it does not, analysis of short term impact will include only very short term follow up for England (ie 6 months after inception of TPD – but midway through. From 2015, SALSUS have produced a ready-merged time-series database from 1996 onwards.

11. Sample size

For the primary outcomes (e-cigarette use), the available data are as follows: In 2013 and 2015, SALSUS collected data from approximately 32,000 young people within S2 (age 13-14) and S4 (age 15-16) classes within 283 schools. Further SALSUS data collection will take place in 2018, with a Scottish Health and Wellbeing Census planned from 2019. HBSC surveys collect data from only 1 class per year group. In 2013, 9,055 young people within 82 schools completed the HBSC Wales survey, including approximately 3600 in the target year groups. The 2015 SHRN survey included 87 schools, including 32000 young people, with approximately 11,000 in the target year groups. By 2017, it is anticipated that 150 schools will provide data as part of SHRN, moving toward inclusion of all secondary schools in Wales in 2019. For the SDDU survey in England, data were collected from 6,000 young people per year, aged 11-16 in 2014. Hence, this includes approximately 2400 per year from the target age groups. From 2016, the survey will be expanded from one class per year group to 3, leading to an estimated increase in sample size to 17,500. Measures of e-cigarette use will be obtained for 2014, 2016 and 2018, with any intervening surveys included, should funding be secured for these (at the time of writing, the survey currently only has funding for 2016 and 2018). For tobacco use, we would go back further, to 1998. This would include SALSUS questionnaires approximately every two years, including approximately 110,000 young people from Scotland and four yearly HBSC Wales surveys including about 14,000 young people, and annual English surveys, including approximately 6,000 young people in 2014, and 17,500 in subsequent years.

We consider the power of our study in terms of the smallest true intervention impact that can be detected: the minimum detectable effect (MDE) for the primary outcome. Guidance on power determination for ITS design varies with some claiming a minimum of eight time periods before and eight after an intervention are required to evaluate changes statistically [68]. If data are not subject to seasonal variation, then at least three data points before and three data points after the intervention are thought to be necessary[69]. Calculations are based on utilising the data available for Wales for seven months pre-intervention (four months in 2013 and three months in 2015) and three months post-intervention (based on tracking to 2017). Fully realised power calculations for estimating detectable effect sizes for extensive ITS designs are not readily accessible. Based on power calculations for a simple step-intervention model, where only an impact on the level of the time-series is expected, and where errors exhibit autocorrelation generated by a first-order autoregressive process[70]: with 80% power and 5% statistical significance for two-tailed tests, the smallest true impact of the introduction of the legislation that can be detected for youth e-cigarette use is 2.20%[71]. Extension of the study to include data in 2019 would enable detection of a minimum effect for youth e-cigarette use of 2.15%. However, the real value in the extra follow-up will be the provision of more power to detect any change in trend, particularly covering the era beyond the transitional period.

12. Statistical analysis

Our study takes the form of an interrupted time series (ITS) design, the strongest quasi-experimental design for studying changes due to a policy[72]. In ITS the impact of the policy intervention is assessed by examining any change in the post-intervention period given the trend in the pre-intervention period. In this way, the underlying trend in the outcome is established and can

be used to estimate the counterfactual, that is, what would have happened if the intervention had not taken place. We shall compare the cross-sectional survey data available before and after the introduction of the intervention to evaluate whether the e-cigarette use outcome among 13 and 15 year old youths deviates from its baseline trend. We shall perform segmented time series regression analysis to control for secular trends and adjust for autocorrelation of the data. For the primary outcome, we shall have individual survey data from certain months in 2013 and 2015 as well as 2017/2019. We shall use logistic regression to model the binary outcome ever e-cigarette use. The basic model for such an interrupted time-series is given by:

$$logit(Y_{ki}) = \beta_0 + \beta_1(time)_{ki} + +\beta_2(intervention)_{ki} + +\beta_3(postslope)_{ki} + \varepsilon_{ki}$$

where Y_{ki} is the e-cigarette use status outcome of individual i at time k; $time$ is a continuous variable indicating time from the start of the study up to the end of the period of observation; $intervention$ is coded 0 for pre-intervention time points and 1 for post-intervention time points and $postslope$ is coded 0 up to the last point before the intervention phase and coded sequentially from 1,2,… thereafter[73]. β_0 estimates the baseline level of the outcome at time 0 (beginning of the period); β_1 estimates the structural trend, independently from the policy intervention; β_2 estimates the immediate impact of the policy intervention or the change in level in the outcome of interest after the policy intervention; and β_3 reflects the change in trend, or growth rate in outcome, after the policy intervention. There will be scope for stratification by/addition of covariates such as sex, age and socioeconomic status. While trends in e-cigarette use are operating in the opposite direction to the secular decline for most substance use behaviours, there are other examples of risk behaviours which are not following this downward trend. Hence causal inference may be improved by demonstrating that any change observed is not observed for an unrelated risk behaviour. Energy drink use is measured within the School Health Research Network (SHRN) survey, and has not followed the secular decline typical of most other psychoactive substances. Hence, we will test whether any interruption to time series occurs in e-cigarette use which is not paralleled by a similar interruption in energy drink consumption.

Analysis of qualitative data

The data will be subjected to thematic analyses using Braun and Clarke's (2006) six step approach. Data analysis and data collection will be conducted in parallel. Philosophically, the analysis will be conducted through an abductive critical realist lens, beginning with exploration of predefined themes derived from the intervention logic model, and pursuing themes which emerge inductively from earlier interviews in later ones. The Cardiff based researcher will code all data, with a sample of interviews second coded by a qualitative researcher in Stirling, with inconsistencies and disagreements resolved through discussion with a third researcher. The full dataset will be stored on a secure Cardiff University server, with subsets of interviews fully anonymised and securely shared with Stirling.

Data integration

The largely qualitative process evaluation will be conducted using harmonised methods across countries and analysed as a single dataset. Analysis will be led in Cardiff and supported by Stirling. The most robust analysis available to test the impact of TPD on vaping rates will be our analysis of the Welsh data, which i) is presented in a monthly format, hence providing multiple time-points within the same survey and ii) includes data on e-cigarette use since 2013, enabling a segmented regression approach. This will be supplemented by a more crude before and after analysis of e-cigarette and tobacco use rates across all 3 countries using an integrated three country dataset, similar to the analysis of changes in child exposure to second-hand smoke after smoke free legislation reported by Moore and colleagues[74]. This analysis will explore whether changes in vaping and smoking rates after TPD are of greater or lesser magnitude in specific UK countries. Because of changes to data collection schedules in Scotland since commencement of the study, these secondary analyses of short term post-legislation changes will be limited to Wales and England, with no post-TPD data on vaping and smoking scheduled for collection until 2018 in Scotland. Longer term analyses will aim to use SALSUS 2018 data, and (subject to access being successfully negotiated) 2019 school census data. This analysis is of course limited by the

constrained number of pre-baseline time-points. These are difficulties which are unavoidable where focusing upon an emerging public health issue such as e-cigarette use for which no long term time series data will be available. Analysis of trends over time in tobacco use, to ascertain whether these have been impacted negatively or positively since the proliferation of e-cigarettes, will represent the most robust test to date of the renormalisation hypothesis which has driven much policy in this area. For these analyses, time-series data on smoking rates across all countries will be pooled into a single analysis, similar to that reported recently by Katikireddi et al. [75] in evaluating impacts of smoke free legislation on youth smoking.

13. Ethical arrangements

The quantitative outcomes dimension of the study will draw upon existing anonymised data sources. The process evaluation protocol was reviewed by the Cardiff University School of Social Sciences Research Ethics Committee in February 2017 and granted approval on March 1st. The 2017 SHRN survey which will be used for quantitative outcomes analysis in Wales received approval at the same meeting.

14. Research governance

The study is sponsored by Cardiff University. The co-investigator team will hold bi-monthly meetings throughout the project to review progress. An independent study steering committee will review study progress biannually, including an independent statistician, who will be asked to review and approve any changes to statistical analysis protocols arising from issues such as emerging changes in policy landscapes in one or more country.

15. Expertise

Graham Moore is Deputy Director of DECIPHer, Cardiff University and Senior Lecturer in Social Sciences and Health. He has expertise in evaluation methodology and tobacco control. He was statistician for a natural experiment to evaluate smoke-free legislation in Wales, and PI on a subsequent replication study which informed Welsh Government's decision to ban smoking in cars carrying children. He was lead author on 2 of the first articles on young people's e-cigarette use. He led the development of MRC guidance for process evaluation and leads DECIPHer's complex intervention methods programme. He will oversee the study as PI, and lead the collation and analysis of young people's datasets. **Linda Bauld** has expertise in policy evaluation with a particular focus on smoking cessation and tobacco control. She authored the UK government's review of the impact of smokefree legislation in England and has led several national evaluations of smoking cessation services in Scotland and England. She chaired the NICE guidance group on tobacco harm reduction and since then has played a central role in establishing and conducting research on electronic cigarettes in the UK in both adults and children. She currently authors a monthly evidence bulletin on e-cigarette studies for Cancer Research UK and recently established the UK electronic cigarette research forum in partnership with Public Health England. Linda is a former scientific adviser on tobacco control to the UK government and chairs the research and evaluation committee of the Scottish Ministerial Group on Tobacco Control. Linda will oversee the Scottish arm of the study. **Britt Hallingberg** is a Research Associate in DECIPHer at Cardiff University. She has published analysis of survey datasets relating to young people's smoking and vaping in Wales. Britt will lead the collation and analysis of youth survey datasets. **Linsay Gray** is a Senior Investigator Scientist at MRC/CSO Social and Public Health Sciences Unit, University of Glasgow and has expertise in the analysis of data from multiple national health surveys with a focus on smoking. She will advise on the design, analysis and conduct of the quantitative study aspects. **Anne Marie MacKintosh** is a Senior Researcher at the Institute for Social Marketing and Centre for Tobacco Control Research at the University of Stirling. Anne Marie has substantial expertise in survey design and analysis, particularly in relation to tobacco and alcohol policy studies. She leads the Youth Tobacco Policy Survey (YTPS), a long-term study evaluating the impact, on young people, of tobacco control policies and remaining tobacco marketing practices. She also leads the quantitative element of the Alcohol Policy Interventions in Scotland and England (APISE) study and is a co-investigator on the Adult Tobacco Policy Survey (ATPS). She will advise on the analysis of survey datasets. **Laurence Moore** has substantial experience in the design and management of complex

mixed-methods evaluation of public health interventions and policies and specific expertise in the analysis of quasi-experimental evaluations of area based initiatives. He will advise the statistical design and analysis and general study conduct. **Marcus Munafò** is a Professor in Biological Psychology, with expertise in addiction. His work has informed policy debates around plain packaging and e-cigarettes. He will advise on study design throughout and will manage the Bristol based RA. **Simon Murphy** is Director of DECIPHer at Cardiff University. He has expertise in the mixed methods evaluation of complex interventions and has conducted a large number of pragmatic national policy trials that have influenced government policy. These include the evaluation of the primary school free breakfasts initiative, that national exercise referral scheme and the social norms and alcohol misuse initiative in universities. He leads the School Health Research Network and the Public Health Improvement Research Network in Wales. He will advise on general study conduct.

16. Partner collaborations

The study will be led from Cardiff University and will involve collaboration with Universities of Bristol, Glasgow and Stirling. The overall study will be overseen from Wales by Graham Moore, the Scottish arm by Linda Bauld and the English arm by Marcus Munafò. Laurence Moore and Linsay Gray at the MRC/CSO Social and Public Health Sciences Unit, University of Glasgow will provide expert advice on methods and statistical analysis.

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