E-cigarette Research Workshops

Summary report

Electronic cigarettes (E-cigarettes or nicotine vapourisers) are a contentious public health issue with different views expressed about any positive or negative consequences of their use. In order to understand current knowledge and research gaps in this area, Cancer Research UK (CRUK), the British Heart Foundation (BHF), the British Lung Foundation (BLF), the Department of Health, the Economic and Social Research Council (ESRC), the Medical Research Council (MRC), and the Wellcome Trust held two workshops in 2015, themed around the mechanisms and outcomes of e-cigarette use. The one-day workshops brought together a varied audience including scientists, health professionals, policy-makers and other stakeholders to discuss the key research priorities that could stimulate the submission of high-quality proposals.

The first workshop, chaired by Professor David Webb (University of Edinburgh), took place in March 2015, and discussed the mechanisms behind e-cigarettes, including the biological effects of nicotine, constituents of vapour, mechanisms for delivery and issues associated with the design and methodology of e-cigarette research The second workshop, chaired by Professor David Lomas (University College London), took place in May 2015, and discussed potential outcomes from e-cigarette, including e-cigarette use patterns, attitudes and behaviours, and longer-term health outcomes.

A list of delegates can be found in the appendix. Although not intended to cover all research topics related to e-cigarettes, the workshops represented an opportunity to identify research gaps. The topics discussed and key questions identified by the workshop delegates are summarised below; these do not necessarily represent the views of the workshop funding partners.

A number of key priority areas for future research were highlighted by the attendees:

1) *Drivers*: What are the exogenous drivers that impact behaviours and perceptions of e-cigarettes (e.g., marketing, regulation, public health messaging etc.)?
2) *Perceptions*: What are the endogenous mechanisms (e.g., attitudes, beliefs, etc.) that influence behaviour for e-cigarette use (e.g., intermittent, regular, dual, non-use)?
3) *Behaviours*: What are the patterns of e-cigarette and tobacco cigarette use in the UK? How effective are e-cigarettes for smoking cessation?
4) *Mechanisms*: What are the biological effects of nicotine and constituents of vapour in e-cigarettes? How does this vary across user and design characteristics (e.g. puff duration, voltage, particle size and density etc)?
5) *Outcomes*: What are the longer-term health outcomes from e-cigarette use (e.g., in pregnancy, quit rates, relapse rates etc. and can we use early biomarkers or existing cohort studies)? What are the potential consequences for vulnerable populations (e.g., pregnant, adolescents, mental health, etc.)?

E-cigarette Research Workshop 1: Mechanisms

Biological effects of nicotine

An overview of the topic area for the biological effects of nicotine was provided by three speakers: Dr Jacques Le Houezec (University of Nottingham); Professor Riccardo Polosa (University of Catania), and; Professor Peter Hajek (QMUL). Table 1 presents the key research questions raised by the workshop attendees during group discussions following the presentations, divided into the subsections of *addiction, health risks* and *sensory appeal*.

Table 1. Key questions arising from discussion around the biological effects of nicotine in e-cigarettes.

Addiction
• How does nicotine dependence differ across different types of nicotine containing products (e.g., nicotine replacement therapy (NRT), e-cigarettes, cigarettes, etc)? • What is the addictive potential of cigarettes versus e-cigarettes and how much is driven by nicotine? • How can we distinguish between addiction versus the appeal of e-cigarettes? • What is the reward-relationship between nicotine delivery in e-cigarettes and other aspects of the devices? • How does genetic predisposition influence nicotine addiction, and how does this differ between individuals who make successful quit attempts using e-cigarettes?
Health risks
• What are the effects of the nicotine in e-cigarettes on the gums and oral tissue? • What are the embryological, developmental and pathological effects of nicotine? • When using e-cigarettes, where is the nicotine delivered? How much of the airways and lungs are exposed and does this vary across e-cigarette devices? • What are the biological effects of nicotine delivery by e-cigarettes for those who have existing pulmonary comorbidity (e.g., COPD)? • Are e-cigarettes a safe 'form' of nicotine replacement therapy for those receiving oxygen therapy (e.g., for lung disease)? • How do the health effects of e-cigarettes compare with medicinal nicotine products? • What are the health effects of nicotine in e-cigarettes for priority groups (e.g., pregnant, adolescents, mental health, etc.)? • How can we distinguish the health effects of nicotine from other constituents of e-cigarette vapour?
Sensory effects
• What is the sensory effect of nicotine and how does this interact with the other e-cigarettes constituents (e.g., flavours). How are these effects best measured and what are the mechanisms of these effects? • What role does nicotine in varying doses versus sensory aspects play in the e-cigarette's addiction potential? How does this differ across brands and types of devices?

Constituents of vapour and mechanisms for delivery

An overview of the topic area for the constituents of vapour and mechanisms for delivery was provided by the following speakers: Dr Maciej Goniewicz (Roswell Park Cancer Institute); Professor Tim Gant (Public Health England); and Louise Ross (Leicestershire Partnership NHS Trust). Table 2 outlines the key questions discussed by the workshop attendees following the presentations, divided into the subsections of *indicators of health risk, second hand risks and other effects* and *design mechanisms.*

Table 2. Key questions arising from the discussion around e-cigarette constituents of vapour and mechanisms for delivery.

Indicators of health risks
• What are the health effects of the different constituents of e-cigarette vapour in the lungs and other systems? How do these vary between brands, device design and user variables (e.g., puff topography, temperature, particle size and density, and changes during storage)? • What is the inhalation toxicity of e-cigarette vapour additives and flavours? How should toxicity be measured and what are acceptable levels of toxicity (e.g., upon thermal degradation, ingestion, etc.)? How does this differ across different devices and populations (e.g., children and young people)? • How do the constituents of e-cigarette vapour affect those with pre-existing conditions (e.g., lung cancer) versus healthy users? Do some constituents (e.g., glycerol) have a protective effect against respiratory infections? • What are the relevant biomarkers to measure and predict the acute and chronic health effects of e-cigarette use, assessing both the e-cigarette overall and individual constituents? How do we translate biomarkers into clinical outcomes?
Second-hand risks and other effects
• Are there second-hand risks of exposure to e-cigarette vapour? How does this differ for different devices and populations (in particular for vulnerable populations)? • How does the vapour from e-cigarettes differ from the constituents in the air? How can the effects of vapour versus naturalistic conditions in the environment be tested? • How does e-cigarette vapour interact with medication (e.g., antipsychotics)? What are the potential pharmacological interactions?
• *Design mechanisms*
• What characteristics of e-cigarettes make users of cigarettes consider switching (e.g., product design, contents, advertising)? • What are the different characteristics of use (e.g., puff duration, voltage, etc.) and how does this vary by product design? • To what extent is the mechanism of e-cigarette vapour delivery oral versus pulmonary and how can these effects be measured?

Study design and methodology

The workshop attendees raised issues relating to study design and methodology for e-cigarette research (Table 3), that should ideally be addressed to produce high-quality research in this area. The challenges of working with the e-cigarette industry, in order for researchers to access and test e-cigarette products in funded studies, and so as to not replicate research in this rapidly evolving area were also discussed (for example COPD issues and drug delivery access have been investigated by researchers in pharmaceutical companies). Researchers should engage with funders to acquire advice on research proposals that may require engagement with the e-cigarette or tobacco industry as the requirements of each proposal will have to be considered on a case-by-case basis. A global integrated research approach across lab, clinical epidemiology, modelling and policy research was recommended in order to inform effective regulatory frameworks for e-cigarettes.

Table 3. Key questions arising from discussion of e-cigarette study design and methodology.

Study design and methodology
• What standardised definitions, methods and tools should be used to assess the function and effects of e-cigarettes (e.g., e-cigarette devices, quantification of measurements, topography machines, animal models, self-report measures)? How can these methods and tools be systematically updated with the development of new e-cigarette devices?
• What tools could be developed to better assess real-world use, content and delivery of e-cigarettes in the laboratory and other settings?
• How can the design of long-term large scale epidemiological studies and short-term smaller trials be developed and standardised? How can standardised designs be effectively disseminated?
• How can populations and within-population factors that moderate the effects of e-cigarettes be identified, and who are the appropriate controls?
• How do we explore any potential biological risks to vulnerable populations (e.g., pregnant women, adolescents, those with mental health issues) and at the same time, explore the potential benefits?
• How can research findings (e.g., from biomarkers) be translated into clinical practice and how can the population level impact be measured?
• How can e-cigarette users be involved further in research?

E-cigarette Research Workshop 2: Outcomes

E-cigarette use, attitudes and behaviours

An overview of the topic area of e-cigarette use, attitudes and behaviours was provided by three speakers: Professor Robert West (UCL); Professor Linda Bauld (University of Stirling and CRUK), and; Professor Amanda Amos (University of Edinburgh). Table 4 presents the key research questions raised by the workshop attendees during group discussions following the presentations, divided into the subsections of *patterns of use, perceptions* and *methodology.*

Table 4. Key questions arising from discussion around e-cigarette use, attitudes and behaviours.

Patterns of use
• Who is using e-cigarettes? How does e-cigarette use differ across populations (e.g., pregnant women, young people, prisoners, hospital patients, older people, those with cancer/other chronic diseases, mental-health problems, low SES, etc.)? How can we measure this? • How are e-cigarettes used by current, former and never-smokers (e.g., to quit, use regularly, dual-use, non-use, relapse patterns)? How does this differ across e-cigarette devices? • How does e-cigarette use impact on other behaviours (e.g., dietary intake, substance misuse)?
Perceptions
• What are the attitudes, knowledge and beliefs about e-cigarettes? How do they affect behaviour? • How do attitudes towards e-cigarettes differ across populations (particularly for young people) and between e-cigarette users or non-users? • What are the perceived risks and benefits of e-cigarette use? How does this compare with perceptions of relative risks for other nicotine products and tobacco cigarettes? • How do different messages (e.g., health messaging, advertisements, peers, family, etc) conveyed about e-cigarettes affect attitudes, knowledge, beliefs and behaviours?
Methodology
• How do we develop standardised definitions, methods and surveys to assess people's attitudes and use of e-cigarettes and how these may change over time? How can these be regularly updated with the development of new e-cigarette devices? • How can the design of longitudinal qualitative and quantitative studies be developed and standardised? How can more standardised designs be effectively disseminated?

Long-term outcomes of e-cigarettes

An overview of the topic area for the long-term outcomes of e-cigarettes was provided by the following speakers: Professor Gerard Hastings (University of Stirling) and Dr Marisa de Andrade (University of Edinburgh); Professor Ann McNeill (KCL), and; Dr Lion Shahab (UCL). Table 5 outlines the key questions discussed by the workshop attendees following the presentations, divided into the subsections of *outcome measures, harm reduction and smoking cessation, and regulations and industry.*

Table 5. Key questions arising from the discussion around the long-term outcomes of e-cigarettes.

Outcome measures
• What are the short and medium term proxies of e-cigarette use that can provide reliable indicators of long-term damage and disease? What are the biomarkers of risk? • How can we develop models and survival analysis to understand the health implications of e-cigarette use for different populations, particularly at risk groups (e.g., pregnant women and their infants)? How can we track this long-term? • How can we add to and enhance existing cohort data to measure the long-term health outcomes of e-cigarette use?
Harm reduction and smoking cessation
• What role can e-cigarettes play in harm reduction regarding second hand smoke? • How effective are e-cigarettes for smoking cessation? How does this differ across e-cigarette devices and populations (e.g., long-term smokers, pregnant women, etc)? • How can cessation opportunities with e-cigarettes be maximised? What aspects in particular brands, device design, and user variables maximise the potential of e-cigarettes in smoking cessation? What is the impact on relapse back to tobacco use? • How do we compare the safety and efficacy of e-cigarettes to other cessation support? How can we measure associations between e-cigarettes and NRT (e.g., for smoking cessation, relapse prevention)? • What information and advice regarding e-cigarettes do health professionals and Stop Smoking Services receive? How can this become more consistent?
Regulations and industry
• How do we assess the impact of regulatory change on motivations and behaviours for e-cigarette use (e.g., flavourings, indoor use, marketing, medical licensing)? How does this differ across groups? What are the likely unintended consequences of regulation? • How can we measure the influence of marketing/advertisements on e-cigarette use across different populations (particularly for young people)? How can we use this information be used for targeted public health interventions/messages? • How can we monitor and understand the strategies of the tobacco industry regarding e-cigarettes (e.g., dual-use, choice engineering)?

Other resources and next steps

Other resources and activities that will support high-quality e-cigarette research were discussed. This included (1) the new UK Electronic Cigarette Research Forum (UKECRF) which has established a network of researchers, policy makers and practitioners to discuss research relating to electronic cigarettes and how current and future research relates to policy and practice. The UKECRF is chaired by Professor Ann McNeill from the UK Centre for Tobacco and Alcohol Studies. In addition, CRUK with the support of the University of Stirling provides a series of monthly updates to give a critical overview of individual studies and put them in the context of what is already known from previous research. (2) The cohort directory, created by MRC in collaboration with BHF, CRUK, ESRC, and Wellcome Trust, that provides a new online directory of the UK's largest population cohorts to help researchers and policymakers find and use them more easily.

In addition, it was noted that due to the expected increase in the number of e-cigarette research proposals, particularly for CRUK's Tobacco Advisory Group, it is essential that the research community engage in peer review processes in this relatively new area to help support the development of high-quality research.

For the next steps, the research community should capitalise on the impetus from the workshops and develop high- quality research proposals, for submission to existing funding streams (see Appendices). Researchers should contact funders to gain advice on the most appropriate funding sources, as funders will only support applications relevant to their remit. The funders will continue to support the research community in its development of quality proposals in this area.

Appendices

E-cigarette Workshop Delegate List

Name	Organisation
Ann McNeill	King's College London
Aki MacFarlane	Wellcome Trust
Alison Cox	Cancer Research UK
Amanda Amos	University of Edinburgh
Ann McNeill	King's College London
Babu Naidu	University of Birmingham
Ben Hawkins	LSHTM
Caitlin Notley	University of East Anglia
Christine McGuire	Department of Health
Clare Hodsdon	Bucks NHS Smokefree Support Service
Clive Bates	Counterfactual
Daisy Gemma Yan Thompson-Lake	QMUL
Daisy Thompson-Lake	QMUL
David Darling	MHRA
David Dorn	Vapourtrails
David Lomas	University College London
David Thickett	University of Birmingham
David Webb	University of Edinburgh
Davinder Dosanjh	University of Birmingham
Elspeth Henderson	Public Health England
Fabia le Moignan	NIHR
Faiza Khan	Kent County Council
Fiona O'May	Queen Margaret University
Fiona Reddington	Cancer Research UK
Fiona Sim	Royal Society of Public Health
George Butterworth	Cancer Research UK
Gerard Hastings	University of Stirling
Gerry Stimson	Imperial College London
Gina Radford	Office of the Chief Medical Officer
Hannah Farrimond	University of Exeter
Heather Rowell	Isle of Wight Council
Helen Hunt	Economic and Social Research Council
Hope Caton	Caton Bell Ltd, Cigbreak
Ian Jarrold	British Lung Foundation
Jacques Le Houezec	University of Nottingham

Jamie Brown	University College London
Jamie Murdoch	University of East Anglia
Jane Landon	UK Health Forum
Jane Luff	Medical Research Council
Jasmine Khouja	University of Bristol
Jennifer Rubin	RAND Europe
Jeremy Pearson	King's College London/British Heart Foundation
Jo Jenkinson	Medical Research Council
John Britton	University of Nottingham
John Clements	MHRA
Jyotsna Vohra	Cancer Research UK
Kamran Siddiqi	University of York
Linda Bauld	University of Stirling/Cancer Research UK
Lion Shahab	University College London
Lorien Jollye	New Nicotine Alliance
Louise Knowles	Department of Health
Louise Ross	Leicestershire Partnership NHS Trust
Lucie Hooper	Cancer Research UK
Lucy Davies	Cancer Research UK
Lynne Dawkins	University of East London
Maciej Lukasz Goniewicz	Roswell Park Cancer Institute
Marisa De Andrade	University of Edinburgh
Martin Dockrell	Public Health England
Mary Yates	South London & Maudsley NHS Foundation Trust
Michael Green	Medical Research Council/University of Glasgow
Michael Ussher	St George's University of London
Mike Knapton	British Heart Foundation
Milica Vasiljevic	University of Cambridge
Nesta Thomas	MHRA
Nick Hopkinson	Imperial College
Nicola Lindson-Hawley	University of Oxford
Nikki Smith	Cancer Research UK
Olatunde Aremu	University of Surrey
Peter Hajek	QMUL
Phil Taverner	NIHR
Rachna Begh	University of Oxford
Ria Poole	Cardiff University
Riccardo Polosa	University of Catania
Richard Holliday	Newcastle Dental Hospital
Richard Roope	RCGP
Robert West	University College London
Sarah Jakes	New Nicotine Alliance UK

Sebastian Lugg	University of Birmingham
Sharon Ogunbiyi	Cancer Research UK
Stephen Knight	Department of Health
Steven Macey	ASH Wales
Sue Cooper	University of Nottingham
Tim Coleman	University of Nottingham
Tim Gant	Public Health England
Tim Jones	CLAHRC West
Victoria Fussey	Department of Health
Wendy Preston	George Eliot Hospital

Funding opportunities for e-cigarette research

Funder	Funding opportunities and areas of interest for e-cigarette research	Website
BHF	All funding streams in principle are available for e-cigarette research, depending on the nature of the scientific question being asked, and the expected costs.	https://www.bhf.org.uk/research/information-for-researchers
BLF	The BLF has no current plans to offer research funding streams targeted specifically at e-cigarette research. However, in principle, all BLF funding streams are open to research grant applications that focus on e-cigarettes and their relationship to the respiratory system. Eligibility will be dependent on the details of the proposed research study and how these fit with the terms of the specific funding stream.	https://www.blf.org.uk/Page/Available-grants
CRUK	Population Research Committee - funding e-cigarette population research, including understanding e-cigarette behaviours, exploring e-cigarettes as an intervention for smoking cessation, and the long-term health effects of e-cigarette use. Tobacco Advisory Group - funding e-cigarette related policy research, including marketing, social attitudes, smoking trends, and policy impacts on e-cigarette use.	http://www.cancerresearchuk.org/funding-for-researchers/applying-for-funding/funding-committees/population-research-committee http://www.cancerresearchuk.org/funding-for-researchers/applying-for-funding/funding-committees/tobacco-advisory-group
ESRC	The Research Grants open call funds awards ranging from £350,000 to £1 million (100 per cent full Economic Cost (fEC)) to eligible institutions to enable individuals or research teams to undertake anything from a standard research project through to a large-scale survey and other infrastructure or methodological development within ESRC's remit.	http://www.esrc.ac.uk/funding-and-guidance/funding-opportunities/3717/research-grants.aspx
MRC	PHIND - public health intervention development scheme. MCMB - oversees the cancer portfolio. Depending on the focus applications could go to NMHB (if neuroscience) or PSMB. Skills development fellowship scheme and other fellowships.	http://www.mrc.ac.uk/funding/browse/public-health-intervention-development-scheme-phind/ http://www.mrc.ac.uk/funding/deadlines/research-board-submission-deadlines http://www.mrc.ac.uk/skills-careers/fellowships/
NIHR	All funding streams in principle are available for applications relating to e-cigarettes, most relevant: Public Health Research (PHR) - evaluate non-NHS interventions intended to improve the health of the public and reduce inequalities in health.	http://www.nets.nihr.ac.uk/programmes/phr http://www.nets.nihr.ac.uk/programmes/hta

	Health Technology Assessment (HTA) - fund independent research about the effectiveness, costs and broader impact of e-cigarettes within the NHS. NIHR is most likely to support studies around the use of e-cigarettes in smoking cessation and impact on health outcomes.	
Wellcome Trust	Seed Awards: Small grants to enable a broad range of possible activities from pilot and scoping studies, to preliminary data gathering and proof-of-principle studies, to planning sessions and meetings of collaborative networks. They are not intended to fund discrete projects with no follow-on plans. Collaborative Awards: Collaborative Awards provide flexible support to excellent groups of independent researchers with outstanding track records. Proposals must address important scientific problems that can only be achieved through a collaborative team effort. Investigator Awards: Investigator Awards provide flexible support at a level and length appropriate to enable researchers to address the most important questions of relevance to human and animal health and disease. Fellowships: We offer a portfolio of personal support schemes to cover the key stages of a research career. All awardees are provided with a salary or stipend, and a budget for research expenses. Support is available for basic biomedical scientists, clinically qualified investigators (including clinical psychologists, dentists and veterinarians) and public health researchers.	http://www.wellcome.ac.uk/Funding/Biomedical-science/Funding-schemes/Seed-Awards/index.htm http://www.wellcome.ac.uk/Funding/Biomedical-science/Funding-schemes/Science-collaborative-awards/index.htm http://www.wellcome.ac.uk/Funding/Biomedical-science/Funding-schemes/Investigator-Awards/WTX059284.htm http://www.wellcome.ac.uk/Funding/Biomedical-science/Funding-schemes/Fellowships/index.htm

Please note: *Applicants are encouraged to contact the relevant office to discuss their ideas and remit. Co-funding opportunities across organisations may be considered on a case-by-case basis.*