What are the research priorities for e-cigarettes?

written by Clive Bates | 27 May 2015



Asking the right questions…

On Thursday 28 May, the second of two workshops on e-cigarette research priorities will be held with a focus on the **outcomes** arising from e-cigarette use, including e-cigarette attitudes and behaviours, and longer-term health outcomes. The meeting is organised by Cancer Research UK, British Heart Foundation, Department of Health, Economic and Social Research Council and Medical Research Council. It is predominantly a scientific gathering, but I will be going and several vapers have been invited to contribute views. It's a very positive initiative in my view. I'd welcome your views:

In advance of the event, the organisers have asked participants to think about the following questions:

> *"For the topic of the e-cigarettes use, attitudes and behaviours the most important question for the progress of e-cigarette research is…"*
>
> *"For e-cigarettes and long-term outcomes, the most important question for the progress of e-cigarette research is…"*

As many of readers of this blog have informed opinions and valuable insights on these matters, I thought would ask for views on these questions or anything else relevant to the research priorities for e-cigarettes… please use the comments to put your point of view or email me.

I'll probably change my mind after listening to the arguments and hearing what everyone else has to say, but for now my own priorities are as follows:

Guiding principles

I think it's worth orientating the discussion with some guiding principles that help to determine what is in scope and what is a distraction…

- **Guiding principle 1**: the research funded by these bodies should inform some useful activity that improves health outcomes – i.e. it informs product or marketing regulation, fiscal strategy, practice in NHS, public health messages or public risk communication. It should not be based on curiosity the mistaken assumption that we need to know everything about these products. Everyone proposing an idea should be able to say: we would use this information to….
- **Guiding principle 2:** the research funded by the bodies should meet a public interest 'additionality' test – that is it should use public or charity money to do things that are not the responsibilities of companies or regulators and would not happen without their involvement. So the research agenda should be designed around the role that public bodies and charities play in society.
- **Guiding principle 3:** the research funded by the bodies should be predicated on careful framing of issues under investigation. For example, when considering 'flavours' and their alleged appeal to adolescents, research should start with an analysis of the pathway by which a flavour could alter behaviour to cause harm, but also the way that the same flavour could be beneficial (if it attracts someone – even a young person – from smoking to vaping). Investment in defining the frameworks in which research is designed and evaluated is a vital prior step to defining any research priorities. (Note: Mike Siegel makes an interesting point about how the US FDA research programme is stacked towards investigating potential negatives).

Research agendas

I prefer to think in terms of a research 'agenda' – a programme of investigation designed to round out understanding of a particular set of issues. Here are four research agendas that matter to me:

1. **Risk perception agenda**: given what is known (and unknown), how should a member of the public think about the risks of vaping, both

compared to smoking and in absolute terms? How do people actually think about the risks vaping? What can be done to bring reality and perception into closer alignment? I think it is particularly important for trusted sources of advice like CR-UK and BHF to be able to speak candidly about risks in a way that serves the public interest and their charitable objectives (i.e. is not highly hedged, risk averse waffle), but to be able to do this with evidence based confidence. I would favour Public Health England having an objective to align risk perception and actual risk – this research agenda would characterise the problem and point the way to solutions.

2. **Nicotine-using population behaviour agenda:** what is the appropriate way to characterise vaping / tobacco / nicotine use and transitions between different types of use? I would like to see well designed surveys that capture smoking and vaping behaviour and its evolution at quite high resolution – not just as an extension of a smoking cessation survey (i.e. to include new vapers and ex-vapers and ex-smokers). This strand of research should be designed to capture supposed unintended consequences such as gateway effects, renormalisation of smoking or reduced quitting – and would require methodological work to achieve that. It should also be designed to capture the converse of these: more quitting, greater denormalisation of smoking, gateway exits etc. This is to provide the basis for confidence or otherwise in regulatory policy at population level.
3. **Adverse policy impacts agenda:** what adverse or unintended consequences could poorly designed regulation, policy or communications have (generally manifest as more smoking than there otherwise would be)? With the introduction of the EU Tobacco Products Directive, the opening of discussions about taxing e-cigarettes, and local measures eg to ban vaping in public places (possible differences within the nations of the UK allowing for natural experiments) can we test that the policies work as intended or conversely that they create unintended consequences. This should be seen as an evaluation of regulatory impacts with a view to improving policy through research. What would be the suite of evaluations that would test the potentially problematic aspects of the EU TPD? We should have baselines in place before May 2016 when the measures start to bite.
4. **'Dual use' agenda:** what are the risks and benefits of smoking and

vaping concurrently? Are there benefits in cutting down and by how much before it makes a material gain? Conversely what are the main risks – does it make people less likely to quit, or more likely? How should we characterise dual use: there is obviously a vast difference between someone who smokes once a month and vapes daily, and someone who vapes once a month and smokes the rest of the time, but both could be considered 'dual users'.

The papers for the meeting include a useful background **summary of US discussions** coming from a 2013 seminar on e-cigarette research priorities hosted by National Institutes for Health. These are interesting with some valuable insights, but in my view focus too much on biomedical / toxicological issues – or as I see that: *finding out a great deal about relatively trivial risks*.

Other areas might include: a few ideas to stimulate thinking: vapers' attitudes and beliefs; personal histories (in lieu of cohort studies); defining and refining insights into 'nicotine addiction'; role of peer support and networks compared to official sources of advice; health economics and NHS cost/saving impact or social cost benefit analysis; smokers preferences in higher resolution (wish to quit, smoke, vape – and *how strongly*?); barriers to switching and reasons for relapsing; the optimum healthcare system interventions (SSS, GPs, campaigns); brief advice interventions at the point of sale (newsagents and vape stores, or online).

More randomised controlled trials (RCTs)?

Also, I would like to see a challenge to the uncritical but widely held assumption that RCTs are the way 'gold standard' method to establish 'efficacy' of e-cigarettes. I am a big fan of RCTs by the way, and not just for drugs, but for any type of intervention where you wish to test the impact of doing one thing differently – for example, using different methods to teach reading in primary schools or offering micro-finance to women in developing countries. But RCTs have limitations in understanding the real world impact, in the way that one might try to establish the impact of a drug on disease or smoking cessation rates. Some issues about RCTs in this field, because the real would behaviour:

- **Not random:** a major consideration about e-cigarettes will be who is willing to use them to try them – if vaping is a 'treatment' route that

appeals to, say, 60% of smokers but using a nicotine receptor partial agonist medicine appeals to only 5% then a straight randomised comparison will be highly misleading. The influences on these preferences are also non-random – including doctors' advice or peer group influence.

- **Not controlled:** in real life the use of e-cigarettes changes over time and will vary according to many uncontrollable influences – people graduate from cig-a-likes to 2nd or 3rd generation devices and may change the strengths and flavours they use over time. They may or may not learn more about vaping or access advice from mentors. There is also constant demotivating negative new flow from public health sources, or new policy developments that change the context in which e-cigarettes are used and understood. For example, over the time that good study would take the perceptions of e-cigarettes risks have changed markedly (for the worse).
- **Not a trial:** Vaping is not one thing, so the investigator needs to ask what is being tested – and in particular if the outcome the investigator is measuring is the one the subject is seeking. Even this is complicated as an individual's the pattern of use often evolves over time, and the reasons and motivations to vape may change – it can be seen as a gradual substitution of one habit for another over a lengthy transitional time. People can start to use e-cigarettes for convenience (using nicotine in places where smoking is banned), but evolve their motivation to include health and wellbeing through cutting down or quitting.

In theory it would be possible to address some of these concerns in study design – but the more that is done, the closer the investigator inevitably comes to observing the real behaviour, in all its multi-factoral complexity.

I am happy to see *good* RCTs done on vaping, but they should be reported and interpreted carefully – with a clear articulation of what feature of vaping is the subject of the controlled trial (the one thing that is varied), and a careful articulation of the limitations of such studies and all the uncontrolled confounders. My view is that greater emphasis should be placed on observational studies – both cross-sectional like the Smoking Toolkit Survey and longitudinal.

Update 29 May 2015. Reflections on the e-

cigarette research priorities event…

I was pretty pleased with the way the seminar went – there were strong evidence-based and convincing presentations from Robert West (PDF), Linda Bauld (PDF), Ann McNeill (PDF) and Lion Shabab, which told a very positive story about the impacts of e-cigarettes at individual and population level. There was also a quite positive and enquiring discussion, with some good exchanges over differences of opinion, that all led to reasonable sense of direction (see below). There were also presentations from Amanda Amos and Marisa de Andrade with Gerard Hastings on the subject of the tobacco industry and renormalisation of smoking by the rise of vaping. The seminar identified four high level themes for research (Drivers, Perceptions, Behaviours, Outcomes). Under each of these themes I've added below some of the things that came up under these headings in discussion, tempered of course by my own views.

1. Drivers

This is about analysing and understanding what external factors shape e-cigarette use and its interaction with tobacco use. Examples:

- **Regulation.** What will the effect of regulation be on use, and ultimately on outcomes? There was particular emphasis on evaluation of the incoming Tobacco Products Directive and having baseline data in place before the directive applies from 20 May 2016 – with tests to theories about its benefits and unintended harmful consequences to be tested.
- **Price & economic drivers.** How do users react to prices and price differentials – what are the relevant price elasticities and cross-elasticities?
- **Marketing.** Is marketing of e-cigarettes beneficial (e.g. driving switching from smoking to vaping and supporting an insurgent product attack a harmful incumbent) or harmful (e.g. by somehow persuading people to smoke)? Are the controls proposed by CAP effective, unduly restrictive or inadequate? What is the impact of the broader bans imposed by the TPD? What sort of marketing innovations will emerge as restrictions bite?
- **Vaping bans.** Will these drive people back to smoking? What is the optimum policy?
- **Health care system behaviour.** What is the ideal way for a health care

system to maximise the opportunity and minimise any risks – i.e. what approach should Stop Smoking Services take to e-cigarettes?

- **Particular populations.** Are there interventions that could work for those in deep poverty, with mental health conditions, held in institutions like prison or psychiatric institutions, or using the NHS?
- **Public messaging.** What is the impact of risk communication of other messages about vaping, coming from public health bodies, the industry, commentators etc
- **Industry.** What is the industry (appropriately segmented) doing? Where are its interests antagonistic to public health and where are its interests aligned? What policies could improve alignment?

2. Perceptions

What are people's beliefs about vaping and smoking? In essence, this theme would explore the *psychological landscape* that underpins nicotine use and behaviour change. Examples:

- **Risk perceptions**. What do users and non-users believe about risks – relative to smoking and relative to other risks in society?
- **Purpose and motivation.** What are people trying to achieve (quitting, smoking differently, avoiding smoking bans, protecting their kids etc) and how committed are they to it?
- **Value propositions.** What do people like and dislike about smoking and about vaping – and how strong are their feelings? What would cause users to switch from one to the other, or to relapse? How important are flavours?
- **Users views.** What do users want, if anything – e.g. from health professionals, health organisations, government, regulators? What regulations are they worried about or pleased about and why?

3. Behaviours

There was high level of support for surveys that extend and deepen our insights into what is actually going on in smoking and vaping and at higher resolution. Examples:

- **Patterns of use and trends.** Systematic collection of data on e-cigarette

use, tobacco use and other forms nicotine use – with careful distinction between intermittent, daily and 'dual use', with better subdivision of dual use. Are e-cigarettes assisting smoking cessation or diverting from it? This could build on the Smoking Tool Kit

- **Type of use.** What types of devices, flavours, strength? Where are people shopping? Are these changing advantageously or adversely over time? Are other uses emerging (e.g. vaping instead of eating a dessert or drinking?)
- **Users.** Who is using what – by age, social-class, gender etc? Are there social class gradients or changing patterns of use in people with mental health conditions?
- **Identifying gateway effects (entries or exits).** Some methodological work needed to design studies that could define and detect any changes in smoking caused by e-cigarettes – for better or for worse?

4. Outcomes

We can't produce a 50 year cohort study to assess health impacts for at least 50 years, but regulatory, fiscal, communications and professional practice decisions need to be made now, what reasonable judgements can be made from what we do know or can learn in the short to medium term. Examples:

- **Direct measurement of short to medium terms impacts on smokers who switch or cut down.** What are measurable impacts on respiratory function, asthma, COPD and cardiovascular events? Are there changes to CVD risk factors (blood pressure, cholesterol etc)?
- **Impact on wellbeing, self-esteem, anxiety etc.** What happens to these important psycho-social indicators when people change from one type of nicotine use to another – and how does this compare to quitting completely?
- **Proxies for overall health impact.** We may not be able to go forward in time, but can we make useful disease risk and life expectancy judgements based on *exposures* to toxins? Are there pitfalls such as non-linear dose-risk relationships?
- **At risk groups.** What if any are the additional risks during pregnancy? Among young people? What should pregnant smokers be told about vaping?

- **Cutting down.** What is the health impact of cutting down or different types of dual use? How much is it necessary to cut down before there is a material gain in health prognosis?

To reiterate – these were the kind of ideas I picked up in the discussions – not the final note of the meeting. All of these need to be tested against the principles set out about and perhaps some drawn together across themes.

Let me know what you think!