

## Appendix 1 – PH45 evidence summary

Summary of new evidence from 2-year surveillance	Summary of new intelligence from 2-year surveillance	Impact
<b>PH45– 01 Recommendation 1 Raising awareness of licensed nicotine-containing products</b> <b>evidence statements 1.1a, 1.1b, 1.1c, 1.2a, 1.2b, 1.3a, 1.3c, 1.4a, 1.4b, 1.4c, 1.5, 1.7, 1.8, 1.9, 2.3.1, 3.3.1, 3.8.3, 4.1.5, 4.1.17, 4.1.18, 4.1.37, 4.1.42, 5.4, 5.5, 5.6; expert papers 1</b>		
<p><b>Effectiveness</b> 20 studies were identified that had assessed the effectiveness of e-cigarettes (ECs);</p> <p>ECs were found to reduce tobacco cigarette consumption and were effective in increasing abstinence at 6 months by 4 systematic reviews that used similar evidence bases<sup>21-24</sup>.</p> <ul style="list-style-type: none"> <li>• A Cochrane systematic review which included 13 studies (2 RCTs and 11 cohort studies) was identified<sup>21</sup>. Results from the 2 placebo comparator RCTs (n=662) indicates that ECs are effective in increasing abstinence from smoking for at least 6 months. However, ECs are no more effective than nicotine patches in 6 month abstinence rates. A higher number of people were able to reduce cigarette consumption by at least half with ECs compared with placebo ECs and compared with nicotine patch. None of the RCTs or cohort studies reported any serious adverse events that were considered to be plausibly related to EC use.</li> <li>• A systematic review which included 6 studies indicated that ECs were more effective for cessation than those without EC-placebos for a 6 month minimum period in smokers (n=1242)<sup>22</sup>. The review also stated that the use of EC was associated with a reduction in the number of cigarettes used.</li> <li>• A systematic review including 6 experimental studies and 6 cohort studies stated that the use of the ECs can reduce the number of cigarettes smoked and withdrawal symptoms, but the adverse events reported are mainly related to a short period of use<sup>23</sup>.</li> <li>• A systematic review, including 6 studies indicated that ECs decreased the desire to smoke, number of cigarettes smoked per day, and exhaled carbon monoxide levels but symptoms of nicotine withdrawal and adverse effects were variable<sup>24</sup>. The</li> </ul>	<p>Intelligence searches and feedback from the topic experts indicated the following:</p> <p><b>New Regulations and Policy</b></p> <p><b>Regulated consumer e-cigarettes</b></p> <p>Currently consumer ECs are regulated by the <a href="#">EU Tobacco Products Directive</a> by the MHRA. This includes restrictions on nicotine levels (20mg/ml) in consumer products, leaflet and packaging requirements and health warnings.</p> <p>In October last year, regulations to protect children made it an offence to sell EC to anyone under 18 or to buy ECs for them came into force.</p> <p>Section 22 of the <a href="#">Committee of Advertising Practice Code</a> was introduced in 2014 and concerns the regulation of advertisements for ECs. This code details the claims that can be made regarding ECs with and smoking cessation.</p> <p>The publication of <a href="#">BSI PAS on e-cigarettes</a> in 2015 – gives guidance for the manufacture, import, labelling, marketing and sale of VP, including ECs, e-shishas and DIY e-liquid mixing kits. The standard covers the purity of e-liquid ingredients, advice on testing the toxicological and chemical analysis of emissions and safety of batteries and chargers.</p> <p>In addition the <a href="#">European Committee for Standardisation</a> (who bring together the National Standardisation Bodies of 33 European countries)</p>	<p><b>New evidence was identified which may change current recommendations</b></p> <p>The guideline currently only recommends licensed nicotine containing products and covers the type, use, cost, supply and availability.</p> <p>At the time of development of PH45 the evidence reviews indicated that there was limited direct evidence available on the effectiveness, quality and safety of ECs (or other products not directly regulated by MHRA), hence the committee did not include consumer ECs as a specified option for tobacco harm reduction. Since then both evidence and policy have moved on to include the following:</p> <p>There is new evidence from 19 studies that indicate that ECs are potentially effective in either reducing cigarette consumption or increasing abstinence rates at periods up to 12 months. Only 1 identified survey of EC use for 30 days indicated that ECs were not associated with decreased cigarette consumption and participants were less likely to quit smoking.</p> <p>The new evidence regarding safety (25 studies) indicates that currently ECs vary widely in their contents but on the whole suggests that ECs are often lower in: toxic content, cytotoxicity, associated adverse effects, and second hand toxicity exposure<sup>50,54-56</sup> than tobacco cigarettes. Whilst there is data on the constituents of both the aerosols generated by ECs and the vaping</p>

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<p>most common adverse effects were nausea, headache, cough, and mouth/throat irritation. Compared with nicotine patches, ECs were associated with fewer adverse effects and higher adherence. Most studies showed a significant decrease in cigarette use acutely; however, long-term cessation was not sustained at 6 months.</p> <p>Evidence from 2 RCTs (n=300, n=657) indicate that ECs result in abstinence from cigarette use at a similar rate to placebo EC<sup>25,26</sup> use or nicotine patches<sup>26</sup>. Similarly smoking reduction was the same in comparison between EC and EC placebo<sup>5</sup>. Whereas, 1 RCT (n=48) indicated ECs are more effective in increasing abstinence compared to control (tobacco cigarettes only)<sup>27</sup>.</p> <ul style="list-style-type: none"> <li>• A 12-month RCT in smokers (n=300) not intending to quit compared 2 nicotine strengths of EC to a non-nicotine placebo model<sup>25</sup>. All groups showed equivalent reduced daily cigarette use at 12 weeks (22.3%) and 52 weeks (10.3%) with complete abstinence from tobacco smoking of 10.7% and 8.7% at week-12 and week-52 respectively.</li> <li>• A randomised-controlled superiority trial in adult smokers (n=657) wanting to stop smoking compared ECs, nicotine patches and placebo (nicotine free ECs) by assessment of biochemically verified abstinence rates at 6 months<sup>26</sup>. Due to the low levels of abstinence achieved in each group 7.3%, 5.8%, and 4.1 for EC, nicotine patches, placebo respectively the study was unable to provide evidence of any superiority of nicotine ECs to patches or to placebo ECs.</li> <li>• A RCT in people unwilling to quit smoking (n=48) indicated that provision of EC for 2 months resulted in 34% of participants stopping smoking tobacco cigarettes compared to no one in the control group<sup>27</sup>. Following on from the randomised period ECs provision for up to 8 months in all study participants resulted in both reduction and cessation of tobacco smoking in almost half of the total study population.</li> </ul> <p>Evidence from 4 observational studies indicate that at 24 months<sup>28</sup>, 12 months<sup>29,30</sup> and 6 months<sup>31</sup> use of EC results in smoking reduction (28%-50%) and abstinence (12.5-62%).</p> <ul style="list-style-type: none"> <li>• The interim results of a cohort study (due to finish in 2019) which</li> </ul>	<p>have started discussions for a European Standard for EC.</p> <p>There is policy support for the use of ECs as a harm reduction approach for smokers from Public Health England with the publication of the PHE <a href="#">E cigarettes an evidence update</a><sup>66</sup>. In addition, a joint statement on ECs by Public Health England and other UK public health organisations <a href="#">E-cigarettes: an emerging public health consensus</a> endorses the use of ECs as a major form of tobacco harm reduction E 'Emerging consensus statement'.</p> <p><b>Licensed e-cigarettes</b></p> <p>The UK MHRA introduced a licensing route for ECs as medicines and manufacturers can apply for a medicinal license (which is required for ECs to be prescribed on the NHS).</p> <p><b>Literature based Evidence</b></p> <p>The experts highlighted the PHE <a href="#">E cigarettes an evidence update</a> as providing a substantial increase in the evidence base in the area<sup>66</sup>. They highlighted 3 publications specifically from within this report as providing important evidence on the use of EC: A PHE publication report <a href="#">Electronic cigarettes</a> - that indicated EC are a safer source of nicotine compared to tobacco cigarettes however they need appropriate regulation, careful monitoring and risk management<sup>67</sup>.</p> <p>A second paper included within <a href="#">E cigarettes an evidence update</a> was stated as been particularly important as it indicated EC are 95% safer than tobacco cigarettes. Taking a Reading - The impact of public health transition on tobacco control and smoking cessation services in England<sup>68</sup>.</p>	<p>liquids data on the short-term health effects are limited and no data was identified on long term health effects.</p> <p>The regulations and standards for ECs as consumer products have or are about to change which will impact on the sale and content and potentially quality of these products.</p> <p>Taken together with the expert feedback that indicated that due to the increased popularity of EC, new published evidence, the unmet need from practice and service users for guidance on their use, it is appropriate for NICE to update recommendations with regard to consumer and licensed ECs.</p> <p>The content of Recommendation 1 impacts significantly on subsequent recommendations. Hence if recommendation 1 is updated and includes EC then the following recommendations should also be considered for update :</p> <ul style="list-style-type: none"> <li>• Recommendation 2-Self-help materials <ul style="list-style-type: none"> <li>○ Advising on non-licensed nicotine-containing products</li> </ul> </li> <li>• Recommendation 3- Choosing a harm-reduction approach</li> <li>• Recommendation 8- Supporting temporary abstinence</li> <li>• Recommendation 10 -staff working in closed institutions</li> </ul> <p>Or additional recommendations made regarding practice advice for EC may also be required.</p>

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<p>is evaluating the safety and efficacy of ECs as a tool of smoking cessation in adults smokers of &gt;1 tobacco cigarette/day (n=491), users of any type of EC, inhaling (n=236), or smokers of both tobacco and ECs (n=232) were identified<sup>30</sup>. At 12 months, ECs users were more likely to be abstinent 62% from tobacco smoking than tobacco smokers (21%) or dual smokers (22%). Adding ECs to tobacco smoking did not reduce tobacco cigarette consumption.</p> <ul style="list-style-type: none"> <li>• The 18 and 24 month follow up of prospective observational study evaluated smoking reduction/abstinence in smokers (n=40) not intending to quit who had received ECs for 6 months was identified<sup>28</sup>. At 24 months a &gt;50% reduction in the number of cig/day was achieved by 28% of the participants. Smoking abstinence was reported in 12.5% participants at 24 months. Additionally 5 subjects stopped EC use (and stayed quit), 3 relapsed back to tobacco smoking and 4 upgraded to more performing products by 24 months.</li> <li>• A proof-of-concept study monitoring modifications in smoking behaviour smokers (n=50) unwilling to quit who switched to using ECs indicated that at 6 months 36% of participants were abstinence from cigarette smoking and smoking reduction was reported for many participants<sup>31</sup>.</li> <li>• A 12-month observational study assessed the impact of ECs on smoking reduction and cessation in smokers with schizophrenia (n=14) not intending to quit. At week 52 50% of participants had a sustained 50% reduction in the number of cig/day and 2% achieved smoking abstinence<sup>29</sup>. Adverse events included: nausea 14.4%, throat irritation 14.4%, headache in 14.4%, and dry cough in 28.6% of participants. However, these adverse events diminished substantially by week-24.</li> </ul> <p>8 cross-sectional or survey based studies from a range of countries including Britain<sup>32, 33</sup>, USA<sup>34 35</sup>, Poland<sup>36</sup> all indicated that EC use was associated with reduced smoking and increased cessation attempts or rates<sup>32-39</sup>. However, 1 comparative 2 time point survey of California smokers suggests that smokers who ever used EC are less likely to decrease cigarette consumption and less likely to quit for 30 days or more<sup>40</sup>.</p>	<p><b>Practice</b></p> <p>The experts also emphasised that there is a feeling from practice that more clarity is required around ECs as they are the most widely used aid in quitting, used by more than a third of smokers in their most recent quit attempt: <a href="#">Electronic cigarettes in England – latest trends</a>. The also highlighted that due to no national guidance practice differed greatly across England. The experts noted that as the recommendations within PH45 make no mention of EC that this undermines the guideline and makes it redundant.</p>	

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<ul style="list-style-type: none"> <li>• A comparative 2 time point web-based survey of British smokers (n=4064) indicated that the daily use of EC while smoking is associated with subsequent increases in rates of cessation attempts and reducing smoking, but not with smoking cessation<sup>32</sup>. Non-daily use of EC while smoking as not associated with cessation attempts, cessation or reduced smoking.</li> <li>• A cross-sectional survey of English adults (n=5863) who had smoked within the previous 12 months and made at least one quit attempt during that period without professional support suggests that EC users were more likely to report abstinence than either those who used NRT bought over-the-counter or no aid to cessation<sup>33</sup>.</li> <li>• An international web-based survey of EC compared dual users (n=3682) (those who use a combination of tobacco cigarettes and EC) with e- cigarette users (n=3530) found that dual users had longer smoking history, lower daily cigarette consumption and similar cigarette dependence compared to cigarette users<sup>37</sup>. Their daily consumption was reduced after initiation of EC use and most used them daily.</li> <li>• A web-based survey of ECs users in Poland (n=179) indicated that almost all participants used ECs daily and were primarily used to quit smoking or to reduce the harm associated with smoking<sup>36</sup>. The survey reported with 66% of those surveyed no longer smoked tobacco cigarettes and 25% smoking fewer than 5 cigarettes a day after using EC.</li> <li>• A survey of individuals who use ECs in USA (n=159) assessed behaviours and perceptions of use<sup>34</sup>. The survey found that an increased duration of ECs use was associated with fewer cigarettes smoked per day and differing patterns of dependence to ECs were contingent upon smoking history.</li> <li>• A cross-sectional survey of adult USA ECs users (n= 215) which utilised biochemically verified smoking cessation reported that 86% of EC users had started vaping as a means of smoking cessation and used e-liquid with nicotine strengths of &lt;20mg/m<sup>35</sup>. Exhaled CO readings confirmed that 66% of the tested sample had quit smoking. Among those who continued to</li> </ul>		

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<p>smoke, mean cigarettes per day had decreased.</p> <ul style="list-style-type: none"> <li>• Findings from a web-based survey of smokers who had tried ECs (n=222) suggest that at 6-months 31% of smokers were abstinence and 67% had reduced the number of cigarettes they smoked and 49% reported abstinence from smoking for a period of time<sup>38</sup>. Of respondents who were not smoking at 6 months, 34% were not using ECs or any nicotine-containing products at the time</li> <li>• A cohort of adult smokers (n=71) making their first purchase at local participating vape shops were followed-up prospectively at 6 and 12 months<sup>39</sup>. At 12 month, 41% subjects could be classified as quitters, 25% as reducers.</li> <li>• A comparative 2 time point survey of California smokers (n=1000) suggests that compared with smokers who never used EC, smokers who ever used ECs were less likely to decrease cigarette consumption and less likely to quit for 30 days or more at follow-up<sup>40</sup>.</li> </ul> <p><b>Safety</b></p> <p>25 studies relating to the safety of ECs use were identified.</p> <p>The evidence from a number of reviews indicates that ECs currently vary widely in their contents and are sometimes inconsistent with labelling<sup>41-45</sup>. Compared to tobacco cigarettes, available evidence suggests that ECs are often substantially lower in: toxic content<sup>43,46,46,47 44,48,49</sup> cytotoxicity<sup>50,51</sup>, associated adverse effects<sup>52,53</sup>, and second hand toxicity exposure<sup>50,54-56</sup>.</p> <p>A number of studies have examined the chemical contents of liquids and assessed the exposures to the chemical contents of the aerosols and produced by ECs with aerosols sometimes containing harmful constituents<sup>41 43,46</sup>. Of potential concern are exposures to propylene glycol and glycerin<sup>43,45,46,48,50</sup>, ethylene glycol<sup>45</sup>, particulates<sup>48,57</sup>, diacetyl and acetyl propionyl (flavourings)<sup>58</sup> and cinnamon flavoured agents<sup>59</sup>, additives (coumarin, acetamide)<sup>45</sup>. Whereas exposure to metals<sup>47</sup>, aldehydes<sup>60</sup>, formaldehyde,</p>		

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<p>acetaldehyde and propionaldehyde<sup>45</sup> were indicated to be minimal in normal vaping conditions.</p> <p>Data on short-term health effects are limited. However, there is indications that ECs use compared to tobacco cigarette smoking reduces asthma exacerbations in individuals with asthma (n=18) who smoke<sup>61</sup> and that the delay in myocardial relaxation caused by acute smoking is not seen with ECs use<sup>53</sup>. Additionally, active and passive tobacco cigarette smoking increases white blood cell, lymphocyte, and granulocyte counts for 1hr but these markers remained unchanged following ECs use in a small study (n=30)<sup>51</sup>. However, aerosol exposure may be associated with respiratory function impairment and increases in exhaled nitric acid<sup>43,62,63</sup>, and serum cotinine levels are similar to those in traditional cigarette smokers<sup>63</sup>. No data was identified on long term health effects.</p> <p>Passive (second hand) exposure to nicotine although lower from EC use than tobacco cigarettes was still found to occur in 2 studies<sup>54,55</sup> but there was no exposure to toxic tobacco-specific combustion products associated with ECs use<sup>55,56</sup>. Likewise third hand exposure from surfaces indicated that EC use could result in exposures to nicotine in 2 studies<sup>64,65</sup> but this was reduced compared to cigarette smoking<sup>65</sup>.</p>		
<p><b>PH45– 02 Recommendation 2 Self-help materials evidence statements 4.1.4, 4.1.10, 4.1.11, 4.1.15, 4.1.17, 4.1.18</b></p>		
<p>No new evidence identified</p>	<p>Topic experts indicated through feedback within the questionnaire that there was a feeling in practice that more clarity is required around EC as they are the most widely used aid in quitting.</p>	<p><b>New evidence was identified which may change current recommendations</b></p> <p>Currently PH45 Recommendation 2 details what self-help materials should provide with regard to the harm-reduction approaches and their health benefits, how to plan a schedule and/or strategy for individuals to cut down and gradually stop or reduce the amount they smoke.</p> <p>Recommendation 2 cross refers to Recommendation 1 on the benefits of using licensed nicotine-containing products to reduce</p>

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		<p>the harm from smoking and type of licensed nicotine-containing products. For ECs this will be limited to those over 18 years old.</p> <p>As the guideline currently does not recommend ECs as an unlicensed option if Recommendation 1 is updated with regard to the use of EC then Recommendation 2 will also require updating.</p> <p>In addition as ECs are widely used in practice the recommendations may need to be updating to provide clarity on their use.</p>
<b>PH45– 03 Recommendation 3 Choosing a harm-reduction approach evidence statements 2.1, 2.1.1, 2.1.2, 3.1.1, 3.1.2, 3.1.3, 3.1.5, 5.1, 5.2, 5.3; expert paper 2</b>		
See new evidence in Recommendation 1	See new intelligence in Recommendation 1	<p><b>New evidence was identified which may change current recommendations</b></p> <p>Recommendation 3 currently outlines the approach, advice and strategies that practitioners should offer to individual who smoke with regard to stopping or harm reduction. With the options available outlined in Recommendation 1.</p> <p>As the guideline currently does not recommend ECs as an unlicensed option then if Recommendation 1 is updated with regard to the use of ECs then Recommendation 3 will also require updating.</p>
<b>PH45 - 08 Recommendation 8 Supporting temporary abstinence evidence statement 3.4.8; expert paper 2</b>		
No new evidence identified	No committee feedback was provided by the expert questionnaire that related to this area. No additional intelligence indicated that this area required updating.	<p><b>Potential impact on recommendation</b></p> <p>This recommendation may require updating if recommendation 1 is changed with regard to the inclusion of ECs as an option for nicotine containing tobacco harm reduction approach.</p>

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<b>PH45 - 09 Recommendation 9 People in closed institutions</b> evidence statement 4.1.7; expert papers 5, 6		
<p>Two studies were identified in populations are potentially at a higher risk of been within closed institutions.</p> <ul style="list-style-type: none"> <li>• A secondary analysis of data from the ASCEND trial (an RCT adult dependent adult smokers motivated to quit (n=657)<sup>26</sup>) compared cessation and smoking reduction outcomes in participants with mental illness n=86 to those without<sup>69</sup>. No differences in smoking cessation rates were identified between either the intervention conditions (nicotine patches, ECs or placebo ECs) or participant status. However, ECs users had higher levels of smoking reduction, treatment compliance, and acceptability.</li> <li>• A 12-month observational study assessed the impact of an ECs on smoking reduction and cessation in smokers with schizophrenia (n=14) not intending to quit. At week 52, 50% of participants had a sustained 50% reduction in the number of cig/day and 2% achieved smoking abstinence<sup>29</sup>. Adverse events included: nausea 14.4%, throat irritation 14.4%, headache in 14.4%, and dry cough in 28.6% of participants. However, these adverse events diminished substantially by week-24.</li> </ul>	<p>Expert feedback from the questionnaire indicated that the more should be done to ensure that there is no inequality for those groups in closed institutions with regard to the effective levels of types of service particularly the use of EC.</p>	<p><b>Potential impact on recommendation</b></p> <p>Recommendation 9 currently provides advice on how staff should ensure individuals within closed institutions can receive tobacco harm support and cross refers to Recommendation 3.</p> <p>Two studies (a secondary analysis from an RCT (n=87) and a small observational study (n=14) indicate that ECs use was acceptable and as effective in smoking reduction and cessation among populations with mental illness as those without.</p> <p>Expert feedback from the questionnaire indicated that the guideline could do more to give appropriate and effective levels of types of service in regard to those inequality groups in closed institutions.</p> <p>This recommendation may require updating if Recommendation 1 and 3 are changed with regard to the inclusion of ECs as an option for tobacco harm reduction approaches.</p>
<b>PH45 - 10 Recommendation 10 Staff working in closed institutions</b> evidence statements 4.1.7, 4.2.6; expert papers 5, 6		
<p>No new evidence identified</p>	<p>No committee feedback was provided by the expert questionnaire that related to this area. No additional intelligence indicated that this area required updating.</p>	<p><b>Potential impact on recommendation</b></p> <p>Currently recommendation 10 cross refers to the options for smoking harm reduction detailed in Recommendations 1 and 3.</p> <p>This recommendation may require updating if Recommendation 1 and 3 are updated with regard to the inclusion of ECs as an option for tobacco harm reduction approaches.</p>
<b>Research recommendations</b>		



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<b>RR – 03 How effective are interventions to help people reduce the amount they smoke (without the intention of stopping)? How great are the health benefits of smoking reduction (by substituting some cigarettes with licensed nicotine-containing products) compared to stopping smoking? What proportion of people who reduce the amount they smoke go on to stop smoking? How soon after starting to reduce the amount they smoke do they stop completely?</b>		
Please see evidence under recommendation 1	Please see intelligence under recommendation 1	

No new evidence was identified that would impact on the following recommendations: 4-7, 11-14, or for research recommendations: 1-2, 4-7.

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