National Institute for Health and Clinical Excellence
Varenicline for smoking cessation

Comment 2: the draft scope

Section	Consultees	Comments	Response
Background information	Royal College of General Practitioners	Good, but it does not summarise the literature on success rates with existing technologies. How high is the bar currently? What are the success rates from existing pharmacological agents alone, counselling alone, and counselling and pharmacological agents in combination with counselling therapies? Adverse effects and cost should be included in this analysis. The key thing here is that drugs should be compared to the best in behavioural interventions including brief counselling. Drugs are expensive., have side effects and monitoring and 'attention' is less than in research settings, leading to lower effect sizes in the real world. So a fair test of a new drug should take all of these factors into account.	The background section of a scope is meant to be an introduction to the disease area and current treatments rather than a critique of all existing treatments. We do not specify the success rates of existing treatments in the background section.
	Pfizer	n/a	n/a
	Royal college of nursing	Seem accurate	Comment noted
The technology/ intervention	Royal College of General Practitioners	Good	Comment noted
	Pfizer	Varenicline now has a marketing authorisation in the UK.	Scope revised accordingly
	Royal college of nursing	Will this intervention be extended beyond those demonstrating a willingness to quit? ....always a difficult one as if there is no willingness to change behaviour the intervention is less likely to be effective.	Public health guidance no 1 states that patient should express desire to quit before treatment is recommended.

Section	Consultees	Comments	Response
	GSK*	Bupropion does not have a licence as an anti-depressant in the UK. It should be referred to as a non-nicotine oral pharmacological treatment for smoking cessation. Bupropion is a selective inhibitor of the neuronal re-uptake of noradrenaline and dopamine. The mechanism by which bupropion enhances the ability of patients to abstain from smoking is unknown, however, it is presumed to be mediated by its dopaminergic and noradrenergic properties acting on the addiction and withdrawal pathways in the brain. The scope states that varenicline works through selectively targeting alpha 4-beta 2 nicotinic receptors in the brain. NRT, by its very nature also binds to nicotine receptors in the brain. It should be noted that the clinical effect of varenciline, NRT and bupropion is to reduce cravings and the related withdrawal symptoms of quitting. The wording is misleading, suggesting only varenicline has these benefits.	The scope does not suggest that bupropion is a licensed antidepressant in the UK or that varenicline is the only treatment that has nicotine-receptor-binding activity.
Population	Royal College of General Practitioners	Pregnant women should be considered separately. Need to specify what's meant by adult, given that 20% 15yr olds smoke, should include adolescents? Releasers with NRT and Buopriorion may be an interesting subgroup. Also, what about concomitant NRT treatment with Varenicline (NRT and Varenicline together for the most addicted?)	Pregnant women cannot be included as varenicline is contraindicated in this group of people. Varenicline has a marketing authorisation for adults only. The common definition of adults is people over the age of 18 in the clinical trials. Potential subgroups are covered under 'other considerations'.

Section	Consultees	Comments	Response
	Pfizer	The Summary of Product Characteristics (SPC) for varenicline states that it is indicated for smoking cessation in adults.	Scope revised accordingly
		In response to your question regarding restricting the population to those expressing a willingness to quit and with regard to the licensed indication for varenicline Pfizer recommends that the population be amended to: "Adults who smoke tobacco products who have indicated a desire to quit smoking."	Scope revised accordingly
		The pivotal trials of varenicline recruited males and females almost equally and the majority of trial participants reported at least one previous serious quitting attempt with nearly half of these using Nicotine Replacement Therapy involving patch and/or gum. This would mean that the results cover all of the potential subgroups identified in the draft scope.	Comment noted
		Please note that the SPC states that varenicline should not be used during pregnancy.	Comment noted
	Royal College of Physicians of Edinburgh	The College suggests that research should attempt to assess the success of varenicline with subjects in different age groups and in relation to measures of nicotine addiction (ie a measure such as the Fagerstrom index), as well as comparing those with previous quit attempts and those who have not attempted quitting previously.	Scope revised accordingly. This has been included under other considerations if evidence allows
	Action Heart	Perhaps an age limit as opposed to 'adult' would be more precise?	Scope revised accordingly
		A potential sub group would be for those individuals that have suffered a vascular disease accident (eg, heart attack/stroke). How soon after an event would patients be able to take advantage of this intervention?	Potential subgroups are covered under 'other considerations'
		Would patients with stable cardiovascular disease be able to use the intervention?	Yes, stable cardiovascular disease is not specified as a contraindication in SPC

Section	Consultees	Comments	Response
	General Practice Airways Group	See comment below relating to willingness to quit	Comment noted
	East Lancashire PCT*	Need to decide whether varenicline should be used in preference to bupropion, or as an alternative. If as an alternative definite criteria should be set as to which one to choose for specific patient groups. Specific information should be given on whether varenicline can be used in those with coronary heart disease, epilepsy, pregnancy, respiratory disease – do the known benefits outweigh the potential risks?	Potential subgroups are covered under 'other considerations'
	GSK*	Please clarify which age group is defined as an adult for the purpose of this review. Efficacy amongst smokers who have previously attempted to quit should be examined. (Durcan MJ. White J. Jorenby DE. Fiore MC. Rennard SI. Leischow SJ. Nides MA. Ascher JA. Johnston JA. Impact of prior nicotine replacement therapy on smoking cessation efficacy. American Journal of Health Behavior. 26:213-20, 2002. Shiffman S, Dresler CM, Rohay JM Successful treatment with a nicotine lozenge of smokers with prior failure in pharmacological therapy, Addiction 99:83-92, 2004.)	The common definition of adults is people over the age of 18 in the clinical trials. Comment noted

Section	Consultees	Comments	Response
	Scharr*	a. Are NICE minded to clarify 'adults' with a lower age limit? b. We have no preference as to population subgroups which should be considered separately. NICE should be aware that Cochrane reviews of smoking cessation interventions have been undertaken for the following subgroups: preoperative (Møller 2005); pregnant (Lumley 2004); hospitalised (Rigotti 2002); COPD (van der Meer 2001); schizophrenia and psychotic disorders (Kumar 2006); and, depression (van der Meer 2006). Full details can be found on the Cochrane Library.	The common definition of adults is people over the age of 18 in the clinical trials. Technology appraisal guidance is normally given inline with the marketing authorisation. Potential subgroups can be considered as mentioned under 'other considerations' and in accordance with the SPC

Section	Consultees	Comments	Response
Comparators	Royal College of General Practitioners	See above; we should ideally include a brief counselling arm as a comparator. An important number of people quit after a brief counselling intervention from a health professional. These smokers do not need to make special trips to re-attend or to visit special clinics or pharmacies. However, not all clinicians use the state of the art behavioural interventions. Spending more on drugs may be a more expensive approach than improving the performance of clinicians through communication skill straining, which might be quite quickly improved say through on line learning. There is a tension here between a 'quick biomedical fix' that turns out to be less effective in real world settings than in research studies with highly motivated and educated participants (e.g. Buopriorion), and the approach which considers the whole person in an ongoing relationship with a trusted practitioners that explores the whole picture with the patient. Smoking is seldom an isolated health threatening behaviour. It usually comes with excessive alcohol, sedentary life style and poor diet. A pill will influence only on of these behaviours and a 'talking'/counselling approach can be generic and influences all of these behaviours. We therefore need to have sophisticated comparisons that take a range of outcomes into account; for example; the numbers receiving an intervention, uptake, effect on other behaviours, the treatment burden and so on. Seeing smoking in isolation of the bigger picture for the patient can lead to false hope about the effect of a pill. Also, training health professionals in the identification of potential beneficiaries of the drug and in motivating them to use it properly may make a big difference to outcomes when compared to clinicians who simply prescribe the drug without additional training in these matters. These are standard comparators. Although Bupropion is probably more effective than NRT, its usefulness is limited by side effects so overall, I don't consider either NRT or Bupropion to be better than the other. Any studies on combination treatments should be included	According to public health intervention guidance no. 1 " brief interventions and referral for smoking cessation in primary care and other settings", patients should only be offered pharmacotherapy if they accept it. Counselling by itself is not considered an appropriate comparator. However advice given in combination with pharmacotherapy has been added to the scope under 'other considerations' Comment noted Scopes revised accordingly

Section	Consultees	Comments	Response
	Pfizer	The two pharmacological interventions currently available on prescription in the United Kingdom are bupropion and nicotine replacement therapy (NRT). NICE has issued guidance on the use of these therapies (TA.39 - Guidance on the use of nicotine replacement therapy (NRT) and bupropion for smoking cessation). The guidance did not preferentially recommend one therapy over the other. As varenicline is a new pharmacological intervention that will be available on prescription in the UK, Pfizer therefore believes that the appropriate comparators should be bupropion and NRT. Although there is a recognised role for behaviour modification programs and counselling in smoking cessation, these are commonly offered alongside pharmacological interventions rather than as an alternative. This would appear to rule out evaluating any pharmacological intervention against them.	Comment noted Comment noted Comment noted
	Royal College of Physicians of Edinburgh	We do not think that any of the existing treatments can be selected as "best alternative care" since the effectiveness of NRT and bupropion is not radically different.	Comment noted
	Action Heart	Will the intervention be assessed both with and without counselling/smoking cessation support? Will the intervention be compared with Nicotine replacement therapies both with and without counselling/smoking cessation support?	Scope revised accordingly Scope revised accordingly

Section	Consultees	Comments	Response
	General Practice Airways Group	Our perception is that bupropion is relatively underused compared to NRT, and suspect this may be due to issues relating to its prescription only status and service provision arrangements rather than clinical or cost effectiveness. The fact that bupropion and varenicline are both prescription only products makes the current use of bupropion a relevant issue, if its prescription only status may create barriers to successful implementation of NICE guidance. It will be important to ascertain whether prescription only status will prove a barrier to implementation of varenicline guidance under current arrangements for NHS smoking cessation services. (see other considerations below) While not another treatment to compare with – we believe it is important that NICE emphasises the important role of support alongside varenicline if this has been an element in all the trials. This will be important to avoid inappropriate use of varenicline. This is relevant from a cost effectiveness perspective since use of varenicline without support may be considerably less cost effective than varenicline with support.	Comment noted Scope revised accordingly
	East Lancashire PCT*	NRT would probably still be seen as the drug of choice. Will NICE consider the trial comparing varenicline versus NRT which is still to report? This will be of great value either way.	The Committee will consider the evidence available at the time of the appraisal.

Section	Consultees	Comments	Response
	Scharr*	a. **Other smoking cessation interventions'** is far too loose. There are 31 Cochrane reviews of interventions for smoking cessations (***excluding*** those relating only to special patient populations). b. NICE should **define a finite number of pair-wise comparisons** that the manufacturer should commit to examine. c. We suggest that this is determined by current NICE guidance: Either Bupropion or Nicotine Replacement Therapy (note not both together) are recommended as part of an abstinent-contingent treatment (ACT), in which the smoker makes a commitment to stop smoking on a target stop date and is given advice and encouragement to do so (Technology Appraisal Guidance No. 38). GPs are supposed to offer brief interventions (opportunistic advice), but the ideal is that the patient will get intensive support, e.g. NHS Stop Smoking Services (Public Health Intervention Guidance No. 1). HEA guidelines (*Thorax* 2000;55;987-999) state that the optimal comparator is ***intensive behavioural support*** plus **NRT or bupropion**). Our local PCTs are implementing NICE guidance, giving: (1) counselling (coping skills; 1:1 or group) with either NRT or Bupropion; (2) counselling alone where the individual refuses drugs. d. It follows that there are **4 broad, suitable comparators** for Varenicline in the NHS setting: • Bupropion plus intensive support • Bupropion plus opportunistic advice • NRT plus intensive support • NRT plus opportunistic advice e. **Different forms of NRT**: In a Cochrane review (Silagy 2004), the ORs for the different forms of NRT were 1.66 (95% CI: 1.52 to 1.81) for gum, 1.81 (95% CI: 1.63 to 2.02) for patches, 2.35 (95% CI: 1.63 to 3.38) for nasal spray, 2.14 (95% CI: 1.44 to 3.18) for inhaled nicotine and 2.05 (95% CI: 1.62 to 2.59) for nicotine sublingual tablet/lozenge. The aggregated OR for abstinence with NRT compared to control was 1.77 (95% CI: 1.66 to 1.88) with only mild heterogeneity across intervention subgroups. These odds were largely independent of the duration of therapy, the intensity of additional support provided or the setting in which the NRT was offered. NICE should note that using NRT gum as the comparator for varenicline would exaggerate the effect size.	a. Scopes include all comparators b. Comment noted c. Comment noted scope has been constructed in accordance with NICE guidance. Advice has been included under other considerations d. Comment noted. A justification of the comparators used will be provided in the manufacturers submission. e. Comment noted

Section	Consultees	Comments	Response
Outcomes	Royal College of General Practitioners	See above; in a perfect world, need to include numbers of consultations, costs, consultation length, effect on other behaviours. Although may expect only limited information to be available on survival.	All relevant costs are included in the economic analysis

Section	Consultees	Comments	Response
	Pfizer	Pfizer recommends that the main outcome measures should cover the success of the intervention as measured by quit rates. The quit rate at 12 months (confirmed chemically) provides the most robust and meaningful of the time points identified in the draft scope. In addition to the twelve month quit rate the three month quit rate provides a valid short-term indication of efficacy.	Comment noted.
		Survival and morbidity related to smoking are not routinely captured in trials of smoking cessation therapies. The link between a reduction in mortality and smoking related morbidity and quitting smoking is established. It is not expected that different therapies would differ in event rates other than by the effect of differential quit rates especially as all prescribed smoking cessation therapies are recommended to be used for limited periods only (between 9 and 12 weeks). Pfizer accepts that the effect on mortality and smoking related morbidity is a factor in decision making by NICE and that differences between therapies (as measured by quit rate efficacy) will be captured within the cost-effectiveness analysis and form part of the QALY measurement.	Comment noted
		NICE guidance TA.39 - Guidance on the use of nicotine replacement therapy (NRT) and bupropion for smoking cessation when evaluating clinical effectiveness used 6 month and 12 month quit rates as the main measure of clinical efficacy.	Comment noted
		Pfizer understands the four week quit rate is a commonly used indicator for the evaluation of the effectiveness of smoking cessation services. This measure cannot be used to judge the efficacy of a pharmacological therapy that involves a minimum 12 weeks of treatment, where length of treatment for comparators varies between 9 weeks and 3 months.	Comment noted
	Action Heart	Will weight gain be measured as this is a common side effect?	Comment noted
	Royal College of Physicians of Edinburgh	These measures are fairly standard. Measures of weight gain in quitters would be valuable.	Comment noted

Section	Consultees	Comments	Response
	East Lancashire PCT*	Absolute statistical values relating to quit rates should be used to inform professionals and patients, not relative risks.	Comment noted
	GSK*	How will quit rate be measured i.e. continuous or absolute abstinence and over what period of time? It is important that this is defined in the scope and used consistently.	Scopes do not usually include this degree of detail. The level of detail will be dependant on the evidence base. Quit rates should be interpreted as including other related measures such as 'continuous abstinence rate', reported in the trials
	Scharr*	a. **Survival:** What does NICE consider a suitable dataset to help the manufacturer's modellers link surrogate outcomes such as 'abstinence at 12 months' with long term survival? b. **Morbidity:** Make explicit – in a good review and model we would expect to see probabilities of individuals moving to states of lung cancer, chronic obstructive pulmonary disease, ischaemic heart disease, cerebrovascular disease and asthma each of which carries a smoking-related cost to the NHS and affects the utility of the individual. c. **Quit rates** at 4 weeks, 6 months, 12 months and longer: NICE should specify whether they require this outcome as self-reported or by carbon monoxide (CO) test? Local PCTs use quit rates at 4 weeks only and these can be self reported if they can't get CO data. Quit rates are fed back to the DH every quarter and we may be able to access them to affirm trial data is realistic.	a. The Institute does not specify evidence for the manufacturer to include/exclude b. Comment noted. This degree of detail will be provided in the manufacturers submission. c. Comment noted, will depend on available evidence

Section	Consultees	Comments	Response
Economic analysis	Royal College of General Practitioners	In the absence of UK trials using Varenicline, I think it is unlikely that robust evidence on cost effectiveness will be produced. Using current data this will need to be a modelling exercise, for example extrapolating quit rates from US trials and applying these to the UK context.	The manufacturer's submission in this STA will address the generalisability of the evidence to the UK context, and will provide an economic analysis relevant to the UK.
	Pfizer	A lifetime time horizon is appropriate	Comment noted
	East Lancashire PCT*	QALYs are likely to be very low in any case.	Comment noted
	GSK*	The model which GSK submitted for HTA No 39 modelled over a 20 year period it would be appropriate for the time horizon for this analysis to be at least as long as this.	Comment noted
	Scharr*	a. The team note that, while Varenicline and Bupropion are available on prescription only, NRT is also available over the counter. If NRT is procured over the counter, then this will significantly reduce the direct costs to the NHS. We cannot see what the relevance of direct costs to the Personal Social Services is aside from if NICE want home-help cases and support for residential care factored in. b. How will the model get from the surrogate outcome 'smoking cessation' to long-term overall survival and QoL? Possible data exists to help with this includes: Anthonisen NR, Effects of a Smoking Cessation Intervention on 14.5-Year Mortality. Annals of Internal Medicine 2005 142: 233-239. c. What allowance will any model make for re-uptake of smoking over the lifetime?	a. Comment noted b. Comment noted c. Comment noted These issues are not suitable for inclusion in the scope.
Other	Pfizer	n/a	n/a

Section	Consultees	Comments	Response
considerations	East Lancashire PCT*	Should varenicline be made available from smoking cessation clinics only? Should any independent prescriber initiate even if they don't have the support of counselling and follow up? Should community pharmacists be encouraged to supply on PGD? Could this be used in combination with bupropion – is there any danger in this? From its mechanism of action you would expect it not to be used with NRT – this needs to be clearly stated.	Public health guidance No. 1 suggests a number of locations where guidance should be offered and procedures when offering advice. This is covered under 'other considerations'
	GSK*	The current scope appears only to cover smoking cessation indication. If the indications were broader than this (eg "prevention of relapse") then the outcome measures would need to be amended to address this. It may be relevant to consider the service implications of any guidance as much of the NRT provided on the NHS is done so through specialised Stop Smoking Services by non-medical prescribers. These services also provide the behavioural support required to help smokers quit.	Comment noted: quit rates should be interpreted as including other related measures such as 'continuous abstinence rate', reported in the trials Comment noted

Section	Consultees	Comments	Response
	General Practice Airways Group	Implementation issues under current NHS smoking cessation services – see under 'comparators' above. Identification of the best pathway of care from initial GP consultation through to quit attempt using varenicline would be useful. Because of the need for support it may be that GPs should be advised to refer the smoker to the smoking cessation service rather than initiate treatment him/herself. However, this brings us back to the prescription only status of varenicline compared to NRT.	According to public health intervention guidance no. 1 "brief interventions and referral for smoking cessation in primary care and other settings", patients should only be offered pharmacotherapy if they accept it. Counselling by itself is not considered an appropriate comparator. However advice given in combination with pharmacotherapy has been added to the scope under other considerations
	Action Heart	Addiction, be it smoking, alcohol, drugs could be seen as a symptom of an unknown underlying cause. Accordingly appropriate 'screening' should be encouraged prior to patients receiving a prescription	Comment noted

Section	Consultees	Comments	Response
Questions for consultation	Royal College of General Practitioners	Unless the smoker has indicated a readiness to try to quit, they are unlikely to take the treatment. So 'readiness to attempt to quit' should be an entry criterion.	Scope revised accordingly
		It would be useful to know if v is more effective than other treatments in those who fail to quit with NRT	Scope revised accordingly
		Studies should be restricted to those examining effectiveness in people prepared to make a quit attempt	Scope revised accordingly
	Action heart	Subgroups – patients with stable/unstable cardiovascular disease.	Covered under 'other considerations'
		Suggest only for patients that are committed to stop smoking unless any evidence already available that suggests otherwise.	Scope revised accordingly
	General Practice Airways Group	Yes – information on the use of varenicline and its effectiveness in subgroups by age and sex and pregnancy status would be extremely useful.	Scope revised accordingly
		We would also be interested in any data relating to the use of varenicline in patients with other major chronic conditions such as COPD/ asthma/ CHD/ diabetes	Scope revised accordingly
		The population NICE considers should be those in which the trials for varenicline have been conducted. We expect that most trials are in people with a willingness to quit. As this is one of the most significant factors in whether people are successful in quitting, we feel it entirely appropriate that only this subgroup of smokers is included in the appraisal.	Scope revised accordingly

Section	Consultees	Comments	Response
	GSK*	*Should the population be specified to those demonstrating a willingness to quit smoking?* This is dependent upon the nature of the clinical trial data and the populations examined. However, it may be argued that any patient that uses a smoking cessation aid is automatically demonstrating a willingness to quit. It may be more appropriate to examine the additional behavioural support which is required in conjunction with the technologies. It is important to consider the nature and level of behavioural support required in conjunction with each of the technologies as this clearly has implications for the relative effectiveness of the interventions as well as demand on services and costs	Scope revised accordingly
Additional comments on the draft scope.	General Practice Airways Group	We feel the issues surrounding implementation are key to ensure that GPs are not inundated with patients wanting to use varenicline, who are not able to access treatment through normal NHS smoking cessation channels.	Comment noted
	GSK*	Please confirm if there will be a scoping meeting for this appraisal. We would be grateful for clarification on the implications of the decision to appraise this technology in a separate appraisal to the review of HTA No 39 which is being carried out within the development of the Provision of Smoking Cessation Services Public Health Guidance. It is not clear how these two pieces of work will be brought together. We are also concerned of the possible implications of varenicline being guaranteed funding (if the STA is positive) whilst NRT and bupropion will no longer have this guarantee since we understand HTA No39 will be withdrawn after the creation of the Provision of Services Guidance.	Scoping workshops are not included in this wave of appraisals Public health and appraisals are co-operating in the production of guidance on varenicline inorder to ensure consistency between guidance documents. The mandatory status of positive technology appraisal recommendations is designed to ensure implementation and uptake to promote best practice, particularly for new technologies, and it is expected that this is achieved within the first few years after the guidance is issued.

Section	Consultees	Comments	Response

Comment 4: Regulatory issues

Section	Consultees	Comments	Action
Remit			
Current or proposed marketing authorisation			

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Welsh assembly government
British Thoracic Organisations*
Royal Pharmaceutical Society of Great Britain*

* Due to administrative issues concerning feedback on the scope these comments arrived after the scheduled deadline.