National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Nalmefene for reducing alcohol consumption in people with alcohol dependence

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Alcohol Concern	Referral to NICE for appraisal is appropriate. The social and financial costs of alcohol dependence on society and the health services in particular are considereable.	Thank you for your comment. At the scoping workshop it was considered that this was an appropriate topic for referral to NICE.
	CSAS	The topic is appropriate.	Thank you for your comment. At the scoping workshop it was considered that this was an appropriate topic for referral to NICE.
	Institute of Alcohol Studies	Patients who are alcohol dependent will, by definition develop alcohol withdrawal symptoms if they stop or suddenly reduce their alcohol intake. If a patient consuming excessive amounts of alcohol does not develop withdrawal symptoms then they would not be classified as alcohol dependent. Lundbeck are, therefore, proposing an intervention in a population of patients --namely 'adults with alcohol dependence who have a high drinking risk level without physical withdrawal symptoms' who do not exist based on current definitions. A number of licensed pharmacotherapeutic agents are available for the	Thank you for your comment. At the Scoping Workshop, it was agreed that the population in the marketing authorisation was comparable to mild alcohol dependence as defined in the NICE clinical guideline CG115. The scope is in line with the marketing authorisation for the

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		management of drinking behaviour in patients who are alcohol dependent These were reviewed in NICE Guideline CG115. The average cost of treatment with acamprosate and naltrexone is of the order of £25.00 per month and their use is cost effective and cost beneficial It was recognised in CG115 that ideally patients with alcohol dependence should be encouraged to abstain fom alcohol but also recognised that this is not always possible. Nevertheless the primary aim of treatment with pharmaco-therapy together with appropriate psychosocial support is to achieve abstinence from alcohol. If nelmafene is to used to control drinking behaviour then this does not differ from the indications for use of the agents already available. However it would appear that the stipulated primary goal of treatment is not abstinence but simply reducing consumption. However, it should be noted that this could be the stipulated aim, if desired, for any of the currently available agents	reduction of alcohol consumption. NICE can only appraise a technology within its marketing authorisation. At the scoping workshop, it was agreed that naltrexone would be included as a comparator in the scope, as it is sometimes used in clinical practice for the reduction of alcohol consumption.
	Lundbeck Limited	Yes, it would be appropriate to refer this topic to NICE for appraisal. Alcohol dependence places a significant burden on NHS resources and healthcare services. Nalmefene is the first and only pharmacological treatment licensed for the reduction of alcohol consumption in adults with alcohol dependence.	Thank you for your comment. At the scoping workshop it was considered that this was an appropriate topic for referral to NICE.
	Royal College of Nursing	Given the current situation where there are increasing numbers of hospital admissions linked to alcohol dependence, with current estimates standing at approximately 1 million hospital admissions each year. The ever growing problem of alcohol dependence nationally and the associated societal, familial and personal issues that this issue causes, means that this topic is appropriate and timely to be reviewed by NICE.	Thank you for your comment. At the scoping workshop it was considered that this was an appropriate topic for referral to NICE.
	Royal College of	Yes	Thank you for your comment. At the scoping workshop it was

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	Pathologists		considered that this was an appropriate topic for referral to NICE.
	Stafford and Surrounds CCG: with input from Solutions for Public Health (SPH) and Public Health colleagues working in Staffordshire County Council (SCC)	(both SCC and SPH) The referral is appropriate	Thank you for your comment. At the scoping workshop it was considered that this was an appropriate topic for referral to NICE.
Wording	Alcohol Concern	Yes	Thank you for your comment. At the scoping workshop it was considered that this was an appropriate topic for referral to NICE.
	Institute of Alcohol Studies	No 1. The population viz alcohol dependent but without physical withdrawal symptoms is not a clinically recognised entity 2. The comparators ought to include the other available pharmacotherapeutic agents 3. A full economic evaluation of the pharmacotherapy for alcohol dependence was undertaken as part of the work in CG115. It is difficult to	Thank you for your comment. 1. At the Scoping Workshop, it was agreed that the population in the marketing authorisation was comparable to mild alcohol dependence as defined in the NICE clinical

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		envisage how an economic evaluation of this drug, for the proposed indication could be undertaken. If the drug is to be prescribed for a set priod of time this might be possible but it is likely that it would be used intermittently which would make any long term evaluation of its efficacy extremely difficult	guideline CG115. 2. At the Scoping Workshop, it was agreed that naltrexone would be included as a comparator in the scope, as it is sometimes used in clinical practice for the reduction of alcohol consumption. 3. The economic evaluation should reflect the full costs and benefits of the treatment for the affected population.
	Lundbeck Limited	The wording of the draft remit is appropriate in our opinion.	Thank you for your comment. No action required.
	Royal College of Pathologists	Wording is appropriate	Thank you for your comment. No action required.
	Stafford and Surrounds CCG: with input from SPH and SCC	(both SCC and SPH) The wording is appropriate	Thank you for your comment. No action required.
Timing Issues	Alcohol Concern	Given the costs of alcohol dependence there is an urgency for a greater range of treatments	Thank you for your comment. NICE aims to schedule appraisals to provide timely guidance to the NHS.
	Institute of	Effective pharmacotherapeutic agents for this indication are already licensed	Thank you for your comment.

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	Alcohol Studies	for use in the UK. Currently they are significantly underused. Thus this appraisal, if it were to go ahead, would not warrent urgent consideration	NICE aims to schedule appraisals to provide timely guidance to the NHS.
	Lundbeck Limited	Nalmefene (trade name, Selincro®) received its marketing authorisation on 27th February 2013 and has been available for NHS prescribing since the beginning of May 2013. Therefore, in order to enable NICE to issue timely guidance to the NHS on the use of nalmefene, we would suggest that this appraisal should proceed as expeditiously as possible.	Thank you for your comment. NICE aims to schedule appraisals to provide timely guidance to the NHS.
	Royal College of Pathologists	Low to moderate urgency.	Thank you for your comment. NICE aims to schedule appraisals to provide timely guidance to the NHS.
	Stafford and Surrounds CCG: with input from SPH and SCC	SCC: There is some enthusiasm to use this product sooner than the proposed timescale for the TA SPH: no comment	Thank you for your comment. NICE aims to schedule appraisals to provide timely guidance to the NHS.
Additional comments on the draft remit	British Association of Psychopharmacology	Didn't receive the Draft remit. However, in terms of appropriateness; alcohol dependence is certainly an appropriate topic for NICE and the continued increases in alcohol-related harm and mortality (e.g., alcohol-related liver disease) means that more robust evidence-based treatments, especially pharmacotherapies, are needed.	Thank you for your comment. The draft remit appears at the top of the scope document. At the scoping workshop it was considered that this was an appropriate topic for referral to NICE.
	Institute of Alcohol Studies	No It does not reflect the 'as needed' aspect of of the proposed dosing schema	Thank you for your comment. The scope document provides only brief details of the technology under

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		In addition, the fact that many patients might moderate their drinking behaviour if advised without the use of medication, which should be tried first, does not seem to have been captured.	consideration. The appraisal will consider the technology within its licensed indication, which would include features of the 'as needed' dosing schema.
	Lundbeck Limited	None	Thank you for your comment. No action required.
	Royal College of Nursing	We consider that the description of alcohol dependence as a condition is not wholly accurate - We would argue that it is not necessarily pre occupation with alcohol. Rather it is a complex interplay of psychological and physiological factors, characterised by elements such as craving, tolerance and withdrawal.	Thank you for your comment. The background to the scope provides an overview of the condition, as described in NICE Clinical Guideline 115.

Comment 2: the draft scope

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Background information	Alcohol Concern	This information is accurate	Thank you for your comment. No action required.
	British Association of Psychopharmacology	The population and treatment details concerning alcohol dependence are accurate, however, there is no real detail of other pharmacotherapies and why nalmefene may be an important alternative	Thank you for your comment. The background information is intended to provide an overview of the condition. No changes made to the scope.
	Institute of Alcohol Studies	Contains too little about the issue in hand --namely the use of pharmacotherapy for relapse prevention	Thank you for your comment. The background information is intended to provide an overview of the condition. No changes made to the scope.
	Lundbeck Limited	The background information given is accurate.	Thank you for your comment. No action required. No changes made to the scope.
	Royal College of Nursing	As per our comment above regarding the acccuracy of the definition of alcohol dependnece. Severity of Alcohol Dependence Questionnaire (SADQ) is referenced here - however AUDIT is the most commonly used tool to initially screen for alcohol related issues and this would be the initial tool of choice which would then be followed by the SADQ if alcohol dependence was indicated by AUDIT. It may be clearer if it is stated that 85,000 people with moderate to severe dependence are treated each year.	Thank you for your comment. The background provides an overview of the condition, as per NICE Clinical Guideline 115. The scope background has been amended to include AUDIT, remove drug misuse, and to include controlled drinking as an aim of intervention.

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		Where substance use is referred to as a co existing mental health disorder, we would remove this. As substance misuse is not technically a mental health disorder and it is misleading to list it here as one. Where it is mentioned that for some people it is possible to reduce their drinking, this again needs clarity. As whilst the initial action is to reduce alcohol intake, going forward this then alters to an outcome of 'controlled drinking' which refers to maintaining alcohol intake on a regular basis at a lower level but in a controlled manner.	
	Royal College of Pathologists	The WHO high drinking risk levels are given, but in addition reference should be made to UK upper recommended limits.	Thank you for your comment. The background information is intended to provide an overview of the condition. The WHO drinking risk levels are included because these are specified in the marketing authorisation for nalmefene. No changes made to the scope.
	Stafford and Surrounds CCG: with input from SPH and SCC	SCC Appears reasonable SPH no comment	Thank you for your comment. No action required.
The technology/ intervention	Alcohol Concern	Yes this was accurate	Thank you for your comment. No action required.

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	British Association of Psychopharmacology	Except for describing that nalmefene has antagonist properties at mainly mu and delta opioid receptors there is no other information regarding the interventions (e.g., when will it be started, dosing regime etc)	Thank you for your comment. The description of the technology is a brief overview. The technology will be appraised within its licensed indication including aspects such as the dosing regimen.
	Department of Health (in consultation with Public Health England)	The proposal, in line with established guidance, that the drug should only be prescribed "in conjunction with continuous psychosocial support…" poses potential problems of clarity. The question is liable to provoke different answers depending on the understanding of how intensive this support needs to be or what should it consist of? If the individual was involved in self-help' support, or 'Tier 2' group work, would that meet the criteria being proposed in the question or does the evidence base suggest the need for structured, care-planned levels of psychosocial support? We suspect the evidence base to which you refer only requires the former to show benefit with nalmafene but if it is possible to be clearer from the current Marketing Authorisation, this may be useful.	Thank you for your comment. The intervention in the scope has been amended to read 'nalmefene in conjunction with psychosocial support (as defined in NICE Clinical Guideline 115)'.
	Institute of Alcohol Studies	Insufficient to determine. Lundbeck's intention is that this medication should be used 'as needed' and so not necessarily as a routine medication ; patients will control their own usage. This is not captured at all in the description of the technology/ intevention.	Thank you for your comment. The description of the technology is a brief overview. The technology will be appraised within its licensed indication.
	Lundbeck Limited	Yes, the description of the technology is accurate.	Thank you for your comment. No action required.
	Royal College of Pathologists	Yes	Thank you for your comment. No action required.

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	Stafford and Surrounds CCG: with input from SPH and SCC	SCC: Appropriate SPH no commentSCC:	Thank you for your comment. No action required.
Population	Alcohol Concern	Yes	Thank you for your comment. No action required.
	British Association of Psychopharmacology	This is, again, very basic. Although some key population details are given (high drinking risk, dependent patients), it is somewhat unclear (without knowing the standatrd treatment regime) how they will find patients who fit this without them also having a need for detoxification and/or displaying physical withdrawal. Does the research team mean to only commence nalmefene on patients after they have finished detox and any detox treatments (e.g., benzodiazepine)?	Thank you for your comment. The scope population has been amended to: Adults with mild alcohol dependence (as defined in NICE Clinical Guideline 115) who have a high drinking risk level (≥ 60 g/day of pure alcohol for men and ≥ 40 g/day for women) without physical withdrawal symptoms and who do not require immediate detoxification. The technology will be appraised within its licensed indication.
	CSAS	'People with alcohol dependence' needs to be defined more precisely. There is a discrepency between the 'high drinking risk level' population specified in the marketing authorisation for nalmefene and the 'medium drinking risk level' population used in the RCTs assessing the effectiveness of nalmefene.	Thank you for your comment. The scope population has been amended to: Adults with mild alcohol dependence (as defined in NICE Clinical Guideline 115) who have a high drinking risk level (≥ 60 g/day of pure alcohol for men

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			and ≥ 40 g/day for women) without physical withdrawal symptoms and who do not require immediate detoxification. At the scoping workshop the manufacturer recognised that nalmefene is indicated for a subgroup of the population in the clinical trials namely those with high drinking risk level.
	Department of Health (in consultation with Public Health England)	There is a typo in word order (high risk drinking level - is intended). The draft scope states that this drug will be aimed at 'adult patients with dependence'. We believe that when this drug was originally discussed, it was aimed at Harmful drinkers and may be primarily aimed at people who continue to drink. There is a risk of misunderstanding here as it seems the drug, whilst it may be aimed at high risk drinkers who recognise this is a problem to control without help (and so meet basic criteria for mild dependence), it does seem mainly to be aimed at reducing consumption and hence may be primarily aimed at the risk of health and other harms of continuing to drink at higher risk levels, and not necessarily primarily the obliteration of mild dependence. The fact that the drug is most effective with those who engage in continuous psychosocial support does not necessarily contradict this, as it seems very likely this high threshold of ongoing attendance could itself motivate reduced consumption, and is likely to include a strong selection bias of engaging mainly the more motivated. Clarity about whether the primary goal is of reducing high risk drinking could be important in identifying who may be best placed to prescribe and for considering likely real-world cost-effectiveness. For patients who currently attend for structured, care-planned support and treatment of their mild dependence, it is possible that nalmafene may be a	Thank you for your comment. At the Scoping Workshop, it was agreed that the population in the marketing authorisation was comparable to mild alcohol dependence as defined in the NICE clinical guideline CG115.The scope population has been amended to: Adults with mild alcohol dependence (as defined in NICE Clinical Guideline 115) who have a high drinking risk level (≥ 60 g/day of pure alcohol for men and ≥ 40 g/day for women) without physical withdrawal symptoms and who do not require immediate detoxification.

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		useful additional option but it appears this might be a very different population from a larger population who could be identified in primary care as high risk drinkers (who may have mild dependence), who might be asked to attend a self-help support group if they want to try a new drug to reduce their consumption (and risk of longer-term health harms). The level of addiction treatment skills needed (and costs) might be very different depending on the nuances of how this population is conceptualised in practise. NICE may benefit in due course by engaging RCGP and RCPsych or other alcohol treatment experts to try and unpick some of these nuances before publishing the final guidance, as responsibility for prescribing for those who are high risk drinkers or mildly dependent may importantly depend on exactly how this population is conceptualised. Recent NICE guidance (CG115) has only recommended the use of pharmacotherapy for those with moderate or severe dependence.	
	Institute of Alcohol Studies	Please see above: dependent patients who do not develp alcohol withdrawal symptoms do not form a clinically identifiable entity. If this appraisal were to go ahead then the population in whom intermnittent medication or patient controlled medication could be considered would be individuals consuming at hazadous/harmful levels who are not yet clinically dependent on alcohol	Thank you for your comment. At the Scoping Workshop, it was agreed that the population in the marketing authorisation was comparable to mild alcohol dependence as defined in the NICE clinical guideline CG115. The scope population has been amended to: Adults with mild alcohol dependence (as defined in NICE Clinical Guideline 115) who have a high drinking risk level (≥ 60 g/day of pure alcohol for men and ≥ 40 g/day for women) without

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			physical withdrawal symptoms and who do not require immediate detoxification.
	Lundbeck Limited	The draft scope correctly defines the patient population for which nalmefene is licensed. However, the nalmefene licence specifically defines the term "high drinking risk level" by reference to World Health Organisation (WHO) guidelines. For clarity, therefore the patient population should be stated as "adults with alcohol dependence who have a high drinking risk level (defined as alcohol consumption ≥ 60g/day for men and ≥ 40g/day for women) without physical withdrawal symptoms and who do not require immediate detoxification."	Thank you for your comment. The scope population has been amended to: Adults with mild alcohol dependence (as defined in NICE Clinical Guideline 115) who have a high drinking risk level (≥ 60 g/day of pure alcohol for men and ≥ 40 g/day for women) without physical withdrawal symptoms and who do not require immediate detoxification.
	Royal College of Nursing	Our concern is whether or not there is a sizeable enough population to make the use of this medication viable. The dependence syndrome is characterised by physical withdrawal symptoms. If symptoms of physical withdrawal are removed then this potentially removes the diagnosis of dependence. We would be interested to know the cost effectiveness of this treatment. If the target audience is for people who do not present with any physical withdrawal symptoms, why introduce a treatment which may cause further dependence? Surely those committed into changing their behaviours will be engaged in psychological therapies? This will also demonstrate their commitment to change.	Thank you for your comment. At the Scoping Workshop, it was agreed that the population in the marketing authorisation was comparable to mild alcohol dependence as defined in the NICE clinical guideline CG115. The scope population has been amended to: Adults with mild alcohol dependence (as defined in NICE Clinical Guideline 115) who have a high drinking risk level (≥ 60 g/day of pure

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		If this drug could be safely used by people with dependence with concurrent physcial withdrawal, but who can reduce their alcohol intake without being at risk of delirim tremens (DTs)/withdrawal seizures, then this means a reduction in alcohol intake can be undertaken with minimal risk of harm. If this medication can be used in such circumstances then this would be far more useful across a wider patient group. Such a patient group would be identified in clinical practice through clinical review, usually undertaken by a prescriber as part of initial assessment either by a medical or non medical prescriber. It may also be appropriate to consider patients who have undergone detox, who have had a requisite period of abstinence usually in the region of 6 months, then wish to drink in a 'controlled' manner. Then it may be of use in this group of patients. We note that the target audience is adults but many services offer treatment for 16 years olds and onwards. How do one measure dependence at such a young age?	alcohol for men and ≥ 40 g/day for women) without physical withdrawal symptoms and who do not require immediate detoxification. The technology will be appraised within its licensed indication which is for reduction in alcohol consumption in adults with alcohol dependence.
	Royal College of Pathologists	It will be necessary to define in more detail what is meant by a high drinking risk level.	Thank you for your comment. The scope population has been amended to: Adults with mild alcohol dependence (as defined in NICE Clinical Guideline 115) who have a high drinking risk level (≥ 60 g/day of pure alcohol for men and ≥ 40 g/day for women)

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			without physical withdrawal symptoms and who do not require immediate detoxification.
	Stafford and Surrounds CCG: with input from SPH and SCC	SCC Not known but looks reasonable SPH People with alcohol dependence' needs to be defined more precisely. There is a discrepency between the 'high drinking risk level' population specified in the marketing authorisation for nalmefene and the 'medium drinking risk level' population used in the RCTs assessing the effectiveness of nalmefene.	Thank you for your comment. The scope population has been amended to: Adults with mild alcohol dependence (as defined in NICE Clinical Guideline 115) who have a high drinking risk level (≥ 60 g/day of pure alcohol for men and ≥ 40 g/day for women) without physical withdrawal symptoms and who do not require immediate detoxification. At the scoping workshop the manufacturer recognised that nalmefene is indicated for a subgroup of the population in the clinical trial namely those with high drinking risk level.
Comparators	Alcohol Concern	Psychosocial intervention is currently the mainstay of treatment for people with 'mild' alcohol dependence	Thank you for your comment. Psychosocial interventions are included as a comparator in the scope.
	British Association of Psychopharmacology	As this is an assessment of a pharmacotherapy it would be beneficial to have a placebo treatment group. Unless there is something specific about the proposed patient population in which other pharmacotherapies are	Thank you for your comment. The comparators in an appraisal are NHS established

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		contraindicated, it would also be very useful to compare nalmefene with another pharmacotherapy (e.g., natrexone, acamprosate).	treatment. At the scoping workshop it was agreed that this was psychosocial interventions. In addition, the comparators have been amended to include naltrexone as this may be used for a reduction in alcohol consumption.
	CSAS	Naltrexone is another opioid antagonist currently used in clinical practice and should be added as a comparator. The licensing conditions state that nalmefene can only be prescribed in conjunction with continuous psychological support focused on treatment adherence and reducing alcohol consumption. The listed comparator of psychological intervention could be defined more clearly to distinguish between pscyhological treatments that are alternatives to treatment with nalmefene and those that would be delivered in conjunction.	Thank you for your comment. The comparators have been amended to include naltrexone. At the scoping workshop it was agreed that psychosocial interventions should be defined as per CG115, but that further differentiation was not needed.
	Department of Health (in consultation with Public Health England)	This drug might be usefully considered along with any other drugs such as naltrexone, which also have some evidence of effectiveness in reductions in consumption in those continuing to drink; and it seems possible that it might have effectiveness in reducing relapse in moderate or severe dependence though that may not be directly relevant in this case.	Thank you for your comment. The comparators have been amended to include naltrexone.
	Institute of Alcohol Studies	Inexpensive, efficacious pharmacotherapeutic agents are already available on the market which could be used in the way it is proposed to use	Thank you for your comment. The comparators have been

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		nelmefene	amended to include naltrexone.
	Lundbeck Limited	Yes, psychological (also known as psychosocial) intervention is the correct comparator for nalmefene in the patient population for which it is licensed. Psychosocial intervention is the mainstay of treatment for people with 'mild' alcohol dependence (NICE Clinical Guideline 115). Mild dependence is the patient population defined in NICE CG115 which best aligns with the licence indication for nalmefene in terms of criteria including level of consumption, diagnosis of dependence and need for assisted withdrawal (detoxification) - this population usually do not require assisted withdrawal. Psychosocial intervention can take many forms. In the nalmefene Phase III clinical trials, psychosocial support was offered to all study participants in a form that is equivalent to the level of an extended brief intervention.	Thank you for your comment. The comparators have been amended to include naltrexone. While it is unlicensed for this indication, attendees at the Scoping Workshop agreed that it is sometimes used off-label for reduction in alcohol consumption.
	Royal College of Nursing	There are other medications that can be used to help people drink at a lower level including naltrexone and acamprosate and so should be compared with these forms of medication as well.	Thank you for your comment. The comparators have been amended to include naltrexone.
	Royal College of Pathologists	Comparators seem appropriate and are in line with other NICE guidance	Thank you for your comment. The comparators have been amended to include naltrexone. While it is unlicensed for this indication, attendees at the Scoping Workshop agreed that it is sometimes used off-label for reduction in alcohol consumption.

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	Stafford and Surrounds CCG: with input from SPH and SCC	SCC No pharmacological comparators are included which might not be appropriate for the group of patients that might be considerd under this TA,.Acamprosate and Disulfiram should perhaps be included SPH Naltrexone is another opioid antagonist currently used in clinical practice and should be added as a comparator. The licensing conditions state that nalmefene can only be prescribed in conjunction with continuous psychological support focused on treatment adherence and reducing alcohol consumption. The listed comparator of psychological intervention could be defined more clearly to distinguish between pscyhological treatments that are alternatives to treatment with nalmefene and those that would be delivered in conjunction.	Thank you for your comment. The comparators have been amended to include naltrexone. While it is unlicensed for this indication, attendees at the Scoping Workshop agreed that it is sometimes used off-label for reduction in alcohol consumption.
Outcomes	Alcohol Concern	The outcomes measures listed are appropriate	Thank you for your comment. No action required.
	British Association of Psychopharmacology	The outcomes are appropriate, although there is no specific mention on looking at issues of compliance, which will have an effect on the listed outcome measures. Evidence shows that nalmefene can be associated with side effects which result in drop out (just as naltrexone research does)	Thank you for your comment. The scope outcomes have been amended to include compliance.
	CSAS	The outcomes from two RCTs of nalmefene (ESENSE1 and ESENSE2) had co-primary outcomes of reduction of the number of heavy drinking days and total alcohol consumption. The listed outcome of 'alcohol dependence symptoms' needs to be further defined to account for the fact that nalmefene is being considered for a population who have a high drinking risk level but without physical	Thank you for your comment. The scope outcomes have been amended to include number of heavy drinking days. Alcohol consumption is included in the scope which would include consideration of total alcohol consumption.

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		withdrawal symptoms. The possibility of avoiding liver function tests with nalmefene needs to be considered in a real life clinical setting, given the prevalence of liver damage in patients who are alcohol dependent.	Scoping workshop attendees agreed that liver function tests are a necessary part of treatment, and that the benefit of reducing the number of tests would be captured in the economic model.
	Department of Health (in consultation with Public Health England)	These are clearly key outcomes. It may be very difficult to evaluate long-term value without considering for how long the treatment should be taken, and how the decision is made when or if to stop. And whether continuous support is still needed if the medication is taken for a prolonged period even after engaging in sustained support. If many of the health and cost benefits are likely to be long-term reductions in consumption and risk, can the outcome analysis reflect this. If treatment services are needed to provide the support, this longer-term outcome analysis becomes even more important.	Thank you for your comment. The scope is intended to provide guidance on the type of outcomes of interest. The time horizon in the economic model should be long enough to capture the costs and benefits of a disease e.g. the duration of the outcomes and timeframe over which costs accrue.
	Institute of Alcohol Studies	The patients for whom this drug is intended will not by definition be alcohol dependent. Thus, 'features of alcohol dependence' would not be a good outcome measure ---unless of course it is envisioned that they might get worse with treatment! Objective measures of alcohol consumption should be included rather than relying on patient reports e.g. serum AST and GGT activities Morbidity should be included as an outcome variable as should hospitalizations	Thank you for your comment. The scope outcomes have been amended to included objective measures of alcohol consumption, morbidity and hospitalisations.

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	Lundbeck Limited	The outcomes measures listed are appropriate and can be demonstrated with direct and indirect evidence from the nalmefene clinical trials.	Thank you for your comment. Workshop attendees considered that the scope should include the following additional outcomes: compliance/concordance, objective measures of alcohol consumption, hospitalisations, controlled drinking, reduction of number of heavy drinking days and morbidity.
	Royal College of Nursing	There needs to be an outcome measure linked to patient specified outcomes. For example the patient outcome could be to drink in a controlled manner, this needs to be included as an outcome to be measured.	Thank you for your comment. The scope outcomes have been amended to include controlled drinking.
	Royal College of Pathologists	Outcomes seem appropriate	Thank you for your comment. Workshop attendees considered that the scope should include the following additional outcomes: compliance/concordance, objective measures of alcohol consumption, hospitalisations, controlled drinking, reduction of number of heavy drinking days and morbidity.

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	Stafford and Surrounds CCG: with input from SPH and SCC	SCC Ok as outcomes, but would also like to see compliance/concordance data. This is likely to be poor in those patients less committed, and failure of treatment due to poor concordance may impact adversly on cost-effectiveness SPH The outcomes from two RCTs of nalmefene (ESENSE1 and ESENSE2) had co-primary outcomes of reduction of the number of heavy drinking days and total alcohol consumption. The listed outcome of 'alcohol dependence symptoms' needs to be further defined to account for the fact that nalmefene is being considered for a population who have a high drinking risk level but without physical withdrawal symptoms. The possibility of avoiding liver function tests with nalmefene needs to be considered in a real life clinical setting, given the prevalence of liver damage in patients who are alcohol dependent. .	Thank you for your comment. The scope outcomes have been amended to include compliance/concordance. Scoping workshop attendees agreed that liver function tests are a necessary part of treatment, and that the benefit of reducing the number of tests would be captured in the economic model.
Economic analysis	Alcohol Concern	None	Thank you for your comment. No action required.
	British Association of Psychopharmacology	Vague. Mentions that the study needs to be long enough to accurately assess differences between nalmefene and standard psychological care but doesn't state what this is.	Thank you for your comment. The economic analysis will be provided by the manufacturer of nalmefene and will be critiqued by an independent academic group. No changes to the scope made.
	Department of Health (in consultation with Public Health England)	Standard treatment of patients who are harmful drinkers or may have mild dependence would be Brief Advice or Brief Treatment lasting only a few sessions. This is bound to be more cost effective than prescribing this drug and associated ongoing psychosocial support.	Thank you for your comment. The costs and benefits of treatments and comparators will be incorporated into the

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			economic model.
	Institute of Alcohol Studies	If the drug is to be prescribed for a set period of time this might be possible but it is likely that it would be used intermittently which would make any long term evaluation of its efficacy extremely difficult	Thank you for your comment. The economic analysis will be provided by the manufacturer of nalmefene and will be critiqued by an independent academic group. No changes to the scope made.
	Lundbeck Limited	We will submit an economic analysis that meets the requirements of the NICE 'reference case'.	Thank you for your comment. No action required.
	Royal College of Pathologists	It will be necessary to define the time horizon. It might be appopriate to consider two time horizons, one relatively short (likely to be months) and one longer (which might require projection of benefits based on persistence of response).	Thank you for your comment. The time horizon in the economic model should be long enough to capture the costs and benefits of a disease.
	Stafford and Surrounds CCG: with input from SPH and SCC	SCC Seems reasonable- the NHS measures however are not identified, but these should include admission avoidance and reduced A&E admissions if considered appropriate SPH no comment	Thank you for your comment. The perspective of the appraisal will include NHS costs which would include NHS admissions and their avoidance.
Equality	Alcohol Concern	We are not aware of any reason why the draft remit and scope would need to be changed in order to address issues of equality.	Thank you for your comment. No action required.
	Institute of Alcohol Studies	This is a stigmatized condition. Confining treatment to individuals who drink excessively who only fall within specific categories could be considered discriminatory.	Thank you for your comment. The attendees at the Scoping Workshop did not identify any

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			potential equality issues affecting people with protected characteristics.
	Lundbeck Limited	We are not aware of any reason why the draft remit and scope would need to be changed in order to address issues of equality.	Thank you for your comment. No action required.
	Stafford and Surrounds CCG: with input from SPH and SCC	SCC No issues with equality, but definitions around the subjective terms used in the scope would be useful in avoiding "indication creep" and early use of this technology as an unintended consequence of the TA SPH no comment	Thank you for your comment. Definitions according to NICE Clinical Guideline 115 have been incorporated into the scope.
Other considerations	Alcohol Concern	None	Thank you for your comment. No action required.
	British Association of Psychopharmacology	The current evidence base on nalmefene is mixed, is it possible to look at these inconsistencies in more detail? Nalmefene may be more effective in certain sub-populations of alcohol dependent patients. Is it possible to target this research to patients who will benefit most, or build in an assessment which will allow more understanding of who is likely to benefit from nalmefene in the future?	Thank you for your comment. At the workshop, the manufacturer stated that people who had a moderate drinking risk level (≥ 40 g/day of pure alcohol for men and ≥ 20 g/day for women) were also included in the trials, so the high drinking risk level ((≥ 60 g/day of pure alcohol for men and ≥ 40 g/day for women) was already a subgroup for the purposes of the marketing authorisation. The attendees agreed that no further subpopulations should

Section	Consultees	Comments	Action
			be specified.
	Institute of Alcohol Studies	The epidemiological evidence on healthy drinking/ low risk drinking. Also the exponential relation between consumption and harms, which means that a reduction of from 9 to 5 units per day suggests a greater health benefit than a reduction from 5 to one/day.	Thank you for your comment. No action required.
	Lundbeck Limited	We do not believe it is appropriate to look at sub-groups of the licensed population. The reason for this is that the regulatory authorities have already determined the sub-population of patients with alcohol dependence for whom nalmefene is suitable (i.e. the nalmefene licence only covers a subgroup of patients; namely, adults with alcohol dependence who have a high drinking risk level without physical withdrawal symptoms and who do not require immediate detoxification). These patients broadly equate to what NICE defines as 'mild' alcohol dependence in its Clinical Guideline 115. Further details on this point are given below in response to the Questions for Consultation.	Thank you for your comment. The attendees of the Scoping Workshop agreed that no further subpopulations should be specified.
	Stafford and Surrounds CCG: with input from SPH and SCC	SCC The TA needs to consider the model of service delivery within the new NHS architecture. Elements of the commissioning and therefore funding responsibility sits with the Local Authority pub;ic health function from April 2013. GPs may be requested to prescribe under shared care, but whether prepared to do this as part of GMS/PMS services remains to be seen. Therefore any CCG costs associated with recharging the LA and GP payments for shared care monitoring, need to be incorporated into the	Thank you for your comment. Service commissioning is beyond the scope of this appraisal. Appropriate Local Government Association will be included in the matrix of consultees for this appraisal.

Section	Consultees	Comments	Action
		costing model SPGH nop comment.	
Innovation	Alcohol Concern	We welcome any new strategies that help to tackle the breadth of alcohol dependence. From what we know about Nalmefene we do consider it be innovative as appears to be a treatment for people not displaying physical withdrawal for whom psychosocial intervention is currently the only widely available option.	Thank you for your comment. The manufacturer may describe the innovative nature of nalmefene in their evidence submission. The Committee may consider this information during the course of the appraisal. No change to the scope required.
	British Association of Psychopharmacology	As mentioned above, the current evidence is mixed. Nalmefene has the potential to be an effective treatment but it may need to be targeted to certain patients (e.g., on the basis of genetic variants, mechanisms of risk).	Thank you for your comment. The manufacturer may describe the innovative nature of nalmefene in their evidence submission. The Committee may consider this information during the course of the appraisal. No change to the scope required.
	CSAS	The management of alcohol dependence needs to be supported by effective, well organised multi-faceted treatment and support. These are commonly organised and provided by community based specialist harm minimisation and recovery services comprising clinical assessment, pharmacological and psycho-social intervention. Nalmefene needs to be assessed in the context of the existing care pathway.	Thank you for your comment. No action required.

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	Institute of Alcohol Studies	No The indication for use of this drug has been 'tweaked' but not sensibly. If the indication, is adapted for e.g. high-risk, non-dependent drinkers then nalmefene would be one of several available drugs that could be used to modify drinking behaviour in this group of individuals	Thank you for your comment. NICE can only appraise a treatment within its licensed indication.
	Lundbeck Limited	Yes, we consider that nalmefene is innovative. Nalmefene is the first and only pharmacological treatment licensed for the reduction of alcohol consumption in adults with alcohol dependence. Psychosocial intervention is the current mainstay of treatment for people with 'mild' alcohol dependence. Nalmefene offers an additional option when psychosocial intervention alone is not sufficient and represents a step-change in the management of these patients, the majority of whom are currently untreated. Because nalmefene enables pharmacotherapy treatment to be applied in a new way to a group of patients where pharmacotherapy is generally not used currently, we believe that it meets the definition of 'innovation' given in '*Innovation, Health and Wealth': "An idea, service or product, new to the NHS or applied in a way that is new to the NHS, which significantly improves the quality of health and care wherever it is applied."(*Department of Health*. Innovation, Health and Wealth.* December 2011)*.* Nalmefene does not require specialist initiation. It can be both initiated and used in primary care and community settings, without any requirement for additional testing beyond what is usually performed for patients diagnosed with alcohol dependence. Moreover, it is anticipated that an appropriate	Thank you for your comment. The manufacturer may describe the innovative nature of nalmefene in their evidence submission. The Committee may consider this information during the course of the appraisal. No change to the scope required.

Section	Consultees	Comments	Action
		psychosocial support could be offered by physicians or other professionals within the same routine appointment. The SAG to the EMA also endorsed the prescribing of nalmefene by GPs/in a primary care setting. This allows patients to access treatment in a setting appropriate to their needs and circumstances. Nalmefene is taken on an 'as needed' basis. This dosing suits the different drinking patterns of each individual and allows the patient to decide when to take their medication. ' As needed' dosing allows patients with alcohol dependence to successfully manage their own treatment to stay in control of their drinking, thus empowering patients to manage their own illness. It may also encourage alcohol-dependent patients to engage with the treatment programme. Experience from the nalmefene clinical trials indicates that the availability of a pharmacological treatment for this type of person with 'mild' alcohol dependence can improve the way that current need is met. Firstly, it encourages the seeking of medical treatment for people with a stigmatised condition, which contains a 'denial' component as part of the addictive nature of the disease. Secondly, the assessment step by a healthcare professional (which includes taking a drinking history and offering brief advice on consumption of alcohol during the initial consultation) can have an effect in itself. In the nalmefene Phase III trials, 35% of patients with a high or very high DRL at baseline reduced their alcohol consumption in the period between the initial visit (screening) and randomisation (Summary of Product Characteristics, SmPC). At randomisation, these patients consumed such a small amount of alcohol that there was little room for further improvement (floor effect).	

Section	Consultees	Comments	Action
		The totality of the product profile for nalmefene, combined with the fact that there is no requirement for specialist initiation or prescribing, supports secondary prevention outcomes in primary care/tier 2 services for mild alcohol dependence, as well helping to achieve existing recommendations in both NICE PH24 and CG115.	
	Royal College of Nursing	If this medication can lead to an increase in patients being able to drink in a controlled manner, this would lead to an additional option for patients with dependence. This increase in choice would lead to a higher likelihood of being able to reduce alcohol associated harms. This has the potential to add to the personalisation agenda by providing patients with an alternative choice in relation to their alcohol recovery.	Thank you for your comment. The manufacturer may describe the innovative nature of nalmefene in their evidence submission. The Committee may consider this information during the course of the appraisal. No change to the scope required.
	Royal College of Pathologists	While the technology is innovative I do not think it represents a step change.	Thank you for your comment. The manufacturer may describe the innovative nature of nalmefene in their evidence submission. The Committee may consider this information during the course of the appraisal. No change to the scope required.
	Stafford and Surrounds CCG: with input from SPH and SCC	SCC No comment SPHThe management of alcohol dependence needs to be supported by effective, well organised multi-faceted treatment and support. These are commonly organised and provided by community based specialist harm minimisation and recovery services comprising clinical assessment,	Thank you for your comment. No action required.

Section	Consultees	Comments	Action
		pharmacological and psycho-social intervention. Nalmefene needs to be assessed in the context of the existing care pathway.	
Questions for consultation	Alcohol Concern	None	Thank you for your comment. No action required.
	British Association of Psychopharmacology	Patients can be categorised as alcohol dependent with a high drinking risk level with simple self-reports and clinical expertise. There are some reviews which question whether nalmefene offers anything substantially different from naltrexone (e.g., Swift, 2013), although they do have some different mechanisims of action and naltrexone may be associated with some mroe severe (although rare) side effects. Acamprosate and disulfiram are other pharmacotherapies which it would be useful to compare with nalmefene. Severity of dependence is a useful coparison to make when determinging the effectiveness of a treatment, however there are otehr possible useful population comparisons (as indicated above)	Thank you for your comment. Alcohol dependence has been defined in accordance with NICE Clinical Guideline 115 in the scope. Naltrexone has been added as a comparator, as it may be used off-label for alcohol reduction. It was agreed that disulfiram and acamprosate should not be included as comparators in the scope.
	Lundbeck Limited	**Question: In which patients would nalmefene be used in clinical practice? How would a population with a high drinking risk level be defined in NHS clinical practice?** As noted above, nalmefene would only be used in adults with alcohol dependence who have a high drinking risk level without physical withdrawal symptoms and who do not require immediate detoxification. A high drinking risk level is defined in the licence as alcohol consumption ≥ 60g/day for men and ≥ 40g/day for women, in accordance with WHO	Thank you for your comment. Alcohol dependence has been defined in accordance with NICE Clinical Guideline 115 in the scope. High drinking risk level has been defined as ≥ 60 g/day of pure alcohol for men and ≥ 40 g/day for women in

Section	Consultees	Comments	Action
		guidelines. There is existing guidance and a number of validated simple assessment tools recommended in NICE PH24 and CG115 (e.g. AUDIT, SADQ, LDQ) which are suitable to assess consumption, dependence and need for assisted withdrawal (detoxification). **Question: Has the most appropriate comparator for nalmefene for the reduction of alcohol consumption in people with alcohol dependence been included in the scope? Should any pharmacological comparators be included?** Yes, as stated above, the relevant comparator for nalmefene in the context of this submission and its licensed indication is psychosocial intervention, which is also in line with NICE clinical guideline 115 and clinical practice. There are no appropriate pharmacological comparators. As noted above: • nalmefene is indicated for the reduction of alcohol consumption only in a precisely defined subpopulation of patients. • This patient group equates to what NICE would describe as 'mild' alcohol dependence in its clinical guideline 115 (NICE, 2011). • Psychosocial intervention is the mainstay of treatment for alcohol dependence, and has been shown to be effective in reducing alcohol consumption (NICE, 2011). • Clinical opinion and practice suggests that patients with alcohol dependence, who do not have physical withdrawal symptoms and do not require immediate detoxification, should be offered a psychosocial intervention. • This is consistent with the NICE guidelines, which indicate that patients with mild alcohol dependence are suitable for a treatment goal of reduction (if they have no significant comorbidity and there is adequate	the scope. The comparators have been amended to include naltrexone. While it is unlicensed for this indication, attendees at the Scoping Workshop agreed that it is sometimes used off-label for reduction in alcohol consumption.

Section	Consultees	Comments	Action
		social support). Existing pharmacological therapies such as acamprosate, naltrexone, or disulfiram are also available to treat alcohol dependence; however, these therapies are licensed for relapse prevention in patients who require immediate detoxification with a treatment goal of abstinence. NICE Clinical Guideline 115 describes these patients as having moderate and severe alcohol dependence. These patients have a more severe form of alcohol dependence than the patients who are eligible for nalmefene and as these patients require immediate detoxification with a treatment goal of abstinence, they are not suitable candidates for nalmefene. **Question: Is the subgroup suggested in 'other considerations appropriate'? Are there any other subgroups of people in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately?** As stated above, the proposed subgroup is not appropriate because the subgroup and level of severity have already been defined/determined via the regulatory process. Nalmefene is only licensed for use in a subpopulation of people with alcohol dependence meeting very specific criteria, as this was the subgroup that the regulatory authorities concluded would benefit most from treatment with nalmefene. During the regulatory process, the European Medicines Agency (EMA) asked Lundbeck to perform subgroup analyses on the Phase III clinical trial data to substantiate the clinical efficacy and clinical relevance of nalmefene and, most importantly, to identify which patients would be most likely to benefit from treatment with nalmefene. A subgroup analysis was performed including patients with high/very high DRL at baseline and who maintained a high/very high DRL at the point of randomisation. The treatment effect in this population was larger than that in the total clinical trial population. The nalmefene licensed indication was,	Scoping Workshop attendees agreed that no subgroups should be specified.

Section	Consultees	Comments	Action
		therefore, based on this sub-population, *as these were the patients who would benefit most from nalmefene*. The Scientific Advisory Group (SAG) to the EMA confirmed that the effect size of nalmefene was clinically meaningful and recognised the validity of the analyses defining the licensed population. Hence, the nalmefene licence has been granted only for a subpopulation of the total Phase III clinical trial population: namely, alcohol-dependent adults with a high/very-high DRL at baseline and who proceeded to randomisation (i.e. who continued to drink at high/very high DRL following the initial screening visit). As these patients broadly equate to what NICE defines as 'mild' alcohol dependence in its Clinical Guideline 115, both the relevant sub-group and the level of severity have already been determined.	
Additional comments on the draft scope	Alcohol Concern	None	Thank you for your comment. No action required.
	British Association of Psychopharmacology	What makes this research difference from other work which has found mixed results?	Thank you for your comment. No action required.
	Lundbeck Limited	None	Thank you for your comment. No action required.
	Stafford and Surrounds CCG: with input from SPH and SCC	If the perceived model of delivery is with GPs under shared care, NICE are adviced to consult with GMC/ LMC to get a view as to whether the opinion is shared.	Thank you for your comment. The commissioning of services is outside the remit of a NICE technology appraisal. No changes to the scope

Section	Consultees	Comments	Action
			made.
	Welsh Government	This HTA only includes adult patients. This will fail to take into account the potential benefit to children and young people, where medication is frequently prescribed off licence, and who are quoted as being in the risk group (from age 16 - although in reality some are younger) This should be considered transparently and preferably included within scope, or at least clear reasons for exclusion given if that is the conclusion. Children's health care is not represented in the consultation groups and I would suggest including RCPCH and the Offices of the 4 UK Children's Commissioners.	Thank you for your comment. The technology can only be appraised within its marketing authorisation, which in this case is for adults.

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

Healthcare Improvement Scotland

NATIONAL INSTITUTE FOR HEALTH CARE EXCELLENCE

Single Technology Appraisal (STA)

Nalmefene for reducing alcohol consumption in people with alcohol dependence

Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:
1.	Add Alcohol Health Network	Lundbeck		Not added	This organisation's interests are not closely related to the appraisal topic and as per our inclusion criteria. Alcohol Health Network has not been included on the matrix of consultees and commentators.

2.	Add CRI	Lundbeck		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. CRI has been added to the matrix of consultees and commentators under 'patient groups'.
3.	Remove Independent Age	Independent Age		Removed	This organisation has been removed from the matrix of consultees and commentators at their own request.
4.	Add Alcohol Academy	Alcohol Academy		Not added	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria. Alcohol Academy has not been included in the matrix of consultees and commentators.
5.	Remove British Association for Services to the Elderly	NICE Secretariat		Removed	This organisation has been removed from the matrix of consultees and commentators at their own request.

6.	Remove British Association of Psychotherapists	NICE Secretariat		Removed	This organisation is now part of the British Psychotherapy Foundation.
7.	Add British Psychotherapy Foundation	NICE Secretariat		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. British Psychotherapy Foundation has been added to the matrix of consultees and commentators under 'professional groups'
8.	Add College of Mental Health Pharmacy	Lundbeck		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. College of Mental Health Pharmacy has been added to the matrix of consultees and commentators under 'professional groups'

9.	Add National Substance Misuse Non-Medical Prescribing Forum	Lundbeck		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. National Substance Misuse Non-Medical Prescribing Forum has been added to the matrix of consultees and commentators under 'professional groups'
10.	Add Substance Misuse in General Practice	Lundbeck		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. Substance Misuse in General Practice has been added to the matrix of consultees and commentators under 'professional groups'
11.	Re-classify Public Health England	NICE Secretariat		Re-classified	This organisation has been re-classified as an 'associated public health group – commentator.'

12.	Re-classify Public Health Wales NHS Trust	NICE Secretariat		Re-classified	This organisation has been re-classified as an 'associated public health group – commentator.'
13.	Add Joseph Rowntree Foundation	NICE Secretariat		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. Joseph Rowntree Foundation has been added to the matrix of consultees and commentators under 'relevant research groups'.