Technology Assessment Report commissioned by the NETSCC HTA HTA 14/151/07 Final PROTOCOL June 2016

1 Title of the project

The clinical and cost effectiveness of lung cancer screening by low dose CT

2 Name of TAR team and project 'lead'

PenTAG, University of Exeter Medical School, University of Exeter

Name: Chris Hyde

Post held: Prof of Public Health and Clinical Epidemiology

Official address: Exeter Test Group, University of Exeter of Medical School, South Cloisters (Room 3.09e), St Luke's Campus, EXETER EX2 1LU

Telephone number: 01392 726051

E-mail address: c.j.hyde@exeter.ac.uk

3 Plain English Summary

- Lung cancer is a serious condition with a poor outlook, causing death before 1 year after diagnosis in the majority of cases.
- It is primarily caused by smoking.
- Although smoking rates are falling, the number of cases of lung cancer will remain substantial for many years because smoking is still common, it takes several years for lung cancer risk to fall after someone has stopped smoking and because there are other causes of cancer e.g. exposure to asbestos. Smoking rates are still rising in developing countries
- Lung cancer can be successfully treated by surgery if it is identified early

- Unfortunately for most people symptoms alerting to the possibility of lung cancer do not occur until the lung cancer is relatively large, and usually too advanced to be removed by surgery
- Using medical imaging to identify lung cancers when they are small before a person has any symptoms ("screening") is thus a logical approach which has been the subject of several trials over the last 30 years
- Traditional chest x-rays have been previously used to screen for lung cancer but were not found to reduce the number of deaths from lung cancer
- However new ways of imaging the lungs such as low dose CT-scanning (computed tomography), which allow the lungs to be seen in 3D, have shown more encouraging results
- There are other tests, at an earlier stage of development, which might be used to screen for lung cancer, but these are not considered in this report
- This piece of research will systematically review the evidence on the effectiveness and cost-effectiveness of screening for lung cancer with low dose CT scanning.
- This will be done by an independent academic group.

4 Decision problem

The research proposed is in response to a brief which requests:

"Could lung cancer screening by low dose CT be cost effective in the UK?"

The general purpose is to provide the National Screening Committee (NSC) with the most up to date evidence on the cost effectiveness of lung cancer screening in the UK.

The components of this question and suggested approach in the briefing document are stated to be:

1. Intervention: Low dose CT screening (LDCT)

2. Patient group: People identified as at 'higher' risk of lung cancer (to be defined and justified)

3. Setting: A secondary care screening service

4. Comparator: No screening

5. Design: A systematic review and meta-analysis of data that includes the findings of the UK Lung Cancer Screening (UKLS) trial, the Nederlands Leuvens Longkanker Screenings Onderzoek (NELSON) trial and other suitable studies. Also, a model of cost effectiveness of lung cancer screening in the UK. Where needed research should include additional systematic reviews to provide robust parameters for a model of clinical and cost effectiveness of screening including the subsequent benefits and harms of investigation and different treatments. Researchers should explore how changes to patient characteristics (e.g. age, sex, smoking history) and the frequency of screening could affect cost effectiveness. Researchers may refine an existing model or develop a new model for this purpose.

6. Outcomes: Potential effect on mortality and QoL as well as cost-effectiveness.

The briefing also suggests that patient level data for NELSON & UKLS may become available during this project and if so, applicants should consider its use.

4.1 Clarification of research question and scope

Having scoped the topic and consulted with clinical experts we agree with this definition of the problem. The detailed approach to each aspect of the study proposed is covered in subsequent sections. At the time of writing it seems unlikely that patient level data for NELSON and UKLS will be available during the course of the project. We anticipate that the main trial results for NELSON will become available during 2016 and the timing of our final report has been planned to allow us to incorporate these results if they are published at the anticipated time.

The scope particularly asks for the high risk of lung cancer population to be defined and justified. This is usually done on the basis of age and smoking history, but has varied considerably between studies which have investigated screening for lung cancer. Thus in the National Lung Screening Trial (NLST) (see below) entry criteria were 55 to 74 years of age at the time of randomization and had a history of cigarette smoking of at least 30 pack years, and, if former smokers, had quit within the previous 15 years. In the NELSON trial (see below) entry criteria were aged 50 to 75 years, who had smoked 15 or more cigarettes per day for more than 25 years (approximately equivalent to at least 18.75 pack years) or ten or more cigarettes for more than 30 years (approximately equivalent to at least 15 pack years), and were still smoking or had quit less than 10 years ago. The UKLS (see below) used a risk prediction model (Liverpool Lung Project (LLP)v2) which combines several items of information including smoking history, a >5% over 5 years risk being defined as “high”.

Both because of the variation in definition of high risk and to give us maximum opportunity to investigate the effect of different levels of risk on effectiveness and cost-effectiveness, we propose to be inclusive with respect to the definition of high risk. Investigators should have indicated they intended to target high risk persons in their study, “high” being judged relative to a base-line risk of a lifelong non-smoker.

Given the need to identify existing cost-effectiveness models to decide whether one should be adapted or a new model developed, we would emphasise the importance of a systematic review of these models. This is reinforced by the knowledge that there have already been several published health economic models, at least one of which has been influential in informing health policy [1].

The brief also asks that research should include additional systematic reviews to provide robust parameters for the model. We note that although this is an ideal, this may not be feasible given the large number of parameters [2]. Systematic reviews will however underpin all the main aspects of clinical effectiveness in the model developed.

4.2 Lung cancer (nature, epidemiology, natural history)

Lung cancer is malignant growth of cells in the lung. There several types of lung cancer but commonly they are split into small cell (SCLC) and non-small cell lung cancer (NSCLC), because they behave in different ways. NSCLC makes up the majority of lung cancer, approximately 80%, and is made up of squamous cell, adenocarcinoma and large cell lung cancer. Squamous cell cancer is the most common type of NSCLC.

The size and spread of the lung cancer when it is diagnosed determines the stage of the cancer ranging from Ia or b to IV. Ia indicates a small cancer less than 3cm in diameter which has not spread. III indicates either a large cancer over 7cm in diameter which has not spread to lymph nodes outside the lung with the cancer in or a smaller cancer which has either spread to lymph nodes outside the lung with the cancer in, or has invaded other structures next to the lung like the chest wall, or are multiple (except where they are in the same lobe of the lung). IV indicates that the cancer is in both lungs or has spread to another part of the body such as the liver or bones or has caused a malignant pleural effusion or pericardial effusion [3].

The prognosis from lung cancer is poor with 1 year survival being in the region of 35% and 5 year survival being in the region of 10% [4]. Survival is slightly better for women than for men. However, smaller cancers with no or limited spread (Stage Ia), have a much better outlook with 5 year survival rates of approximately 50% [5]. Thus the poor overall survival rate occurs because lung cancers grow rapidly and do not cause symptoms for a patient until the lung cancer has grown to a large size and/or spread. Just under 80% of lung cancers present at Stage III and IV and the 5 year survival rate for Stage III and IV cancers is very poor, <10%.

The treatment options for different types and stages of lung cancer are summarised by NICE [6]. Treatment also depends on whether a patient is fit enough to undergo a treatment option such as surgery, and patient preference. In general, treatments with curative intent such as surgery to remove the cancer, radiotherapy and radio-chemotherapy are targeted at early stage lung cancers. Less intense radiotherapy and chemotherapy can also be used with other palliative treatments where the intent is not curative, where the stage of the cancer is advanced or the patient is frail. Decisions on diagnosis and treatment are complex and are made by specialist multi-disciplinary teams. The number of treatment options has increased markedly over the last two decades.

The main cause of lung cancer is smoking and it is estimated that 85% of lung cancer is attributable to smoking, and would be avoidable if smokers had never smoked [7]. If someone stops smoking their risk of lung cancer reduces, approximately halving after 10 years of cessation. However, even after 30 years it may still remain elevated relative to someone who has never smoked at all [8]. On average however, the more cigarettes are smoked and the greater the number of years that someone has smoked for, the greater the risk of developing lung cancer. Preventing smoking and supporting smoking cessation are thus the most important things that can be done to reduce new lung cancer cases and have thus received much emphasis. Smoking cessation also brings benefits from avoiding other smoking related diseases e.g. coronary heart disease, cerebro-vascular accidents and chronic obstructive pulmonary disease. There are other causes of lung cancer such as exposure to asbestos and silica, but these make a very small contribution to the number of lung cancer cases. Age is an important risk factor, but is not amenable to intervention. Nearly 50% of lung cancer deaths occur in the over 75 age group.

Unfortunately past high rates of smoking combined with poor prognosis make lung cancer a continuing major personal and public health problem. 44,500 cases of lung cancer were diagnosed in the UK in 2012; this is 13% of the total number of cancer cases; it is the second most common cause of cancer; however, it is the most common cause of cancer death – 35,400 in the UK in 2012. The global number of lung cancer deaths is estimated to be 1.6 million [9]. The situation is similar in other developed countries and is likely to worsen in developing countries where rates of smoking are still

rising. In developed countries although rates of getting lung cancer and dying from it are falling, the rate of decline is slow or not falling at all in some sub-groups, particularly women [10]. This combined with continued smoking by a substantial minority in the population (19% in 2013 [11]) and the time taken for risk to reduce after stopping smoking means that lung cancer will remain a substantial public health problem for the foreseeable future.

4.3 Screening for lung cancer

Given that treatment for lung cancer is relatively successful when the tumours are small and have not spread, and that early stage tumours rarely cause symptoms which would prompt people to seek medical care, screening has long been seen as a logical approach to trying to reduce the effects of lung cancer. Screening involves testing people with no symptoms to detect the cancers at an early stage. It could be targeted at all members of the population, or more commonly is focused on sections of the population at greatest risk, defined by characteristics such as age or sex. In the case of lung cancer the number of years of smoking would be another important risk factor to identify those persons most likely to develop lung cancer and so be screened with greatest chance of benefit. Over several decades a number of potential screening tests have been investigated including chest x-rays (CXR) and sputum cytology. Neither of these has been found to be effective in studies designed to test this with least risk of bias, randomised-controlled trials (RCT) [12].

As CT scanning has developed and offered progressively improved images at lower radiation dosage, so it has become the test offering the greatest potential for effective and cost-effective screening for lung cancer with much research devoted to investigating whether this is the case (see below). Special tests of blood, sputum and breath have also been considered but research to measure their effectiveness is at a much earlier stage of development [13].

A major challenge in all screening is that virtually no test is completely accurate. This means that any screening will incorrectly categorise some individuals who truly have the disease as not having it (false negatives) and incorrectly categorise some individuals who are disease free as having the disease (false positives). Tests for lung cancer are not an exception. As a consequence the benefits flowing from earlier identification and treatment of disease in some individuals will always need to be off-set by the likelihood that there will be some false negatives who may be falsely reassured. There will also be a number of patients found to be false positives who will require further investigations and possibly experience anxiety relative to the situation where no screening takes place. The problem of false positives is frequently magnified in screening because the incidence of the cancer being detected is often still low in the screened population , so apparently accurate tests, particularly in terms of their specificity, generate large absolute numbers of false positives.

4.4 Technology of interest

CT scanning was one of the major medical advances in the 20th century, and its development continues. It makes use of computer-processed combinations of many x-ray (XR) images taken from different angles to produce cross-sectional (tomographic) images (virtual 'slices') of specific areas of a scanned object, allowing the user to see inside the object without cutting [14].

Since the first commercially viable CT scanner was invented by Sir Godfrey Hounsfield in the 1960's, CT scanning has developed in a number of ways, notably the number of the detectors, the speed with which data can be acquired and the sophistication of the computer reconstruction techniques.

Reduction in the amount of radiation required to provide an acceptable image for initial diagnostic purposes, has also reduced so that a LDCT scan requires an effective radiation dose of 0.3-0.6 millisieverts (mSv). In the UK, the average annual exposure, including background and medical applications, is about 2.7 (mSv) of radiation a year [15]. Training and quality control are critical in achieving high quality images while minimising XR exposure.

Lung CT scans detect discrete pulmonary nodules as the most common abnormality that may be suggestive of malignancy, but abnormal scarring and ground glass opacities may also seen as worrying features and potentially recognised as malignant changes. Features that assist in differentiating benign from malignant lesions include fat within the nodule and calcification. Nodules suspicious of malignancy are often referred to as non-calcified nodules, but calcification is not a guarantee that the nodule is not cancerous. Size is also important in determining the likelihood that a non-calcified nodules is malignant, and large lesions are more likely to be malignant than small ones [16]. Analysis from one CT screening study reported that, of 378 positive baseline screening CTs identifying non-calcified nodules < 5 mm, none proved to be malignant on further investigation. In contrast, 3.3% of those 5–9 mm and more than 50% >= 10mm proved to be malignant [17]. Unfortunately the same series noted that more than 90% of CT nodules were benign. However, major advances in the reporting of CT detected nodules have been made over recent years and the use of volumetrics (calculating the volume of a nodule and the volume doubling time) has improved the accuracy of LDCT. This was used by the NELSON and the UKLS trials, but the NLST used the diameter of the nodules alone.

An important issue is that LDCT scanning screening for lung cancer is not a homogenous technology, so careful attention needs to be paid to the exact nature of the device being used, the protocol being used and precise criteria being employed to define an abnormality as potentially malignant, benign or indeterminate. In a screening programme this needs to take into account the possibility that screening scans may be repeated and stability of abnormalities over time may be part of the criteria indicating a possible cancer. The further management of each category, particularly further investigation, also needs to be specified as part of the definition of the technology.

4.5 Clinical pathway (in presence and absence of screening)

The normal clinical pathway in the absence of screening is that people will present with symptoms such as persistent cough, haemoptysis, or persistent breathlessness which will then be investigated with CXR, CT scanning, bronchoscopy and biopsy. The initial symptoms of lung cancer are commonly associated with smoking, so a problem for individuals is judging whether their cough is the same or worse than usual. The investigations not only potentially confirm lung cancer, but also, if confirmed, are used to stage it. If the stage is low (I or II) and a patient is fit for surgery, this will generally be the treatment option. This may be followed by radiotherapy and chemotherapy depending on whether the patient has metastases. The intent will usually be curative. If the Stage is high (III or IV), the intent of further treatment is palliative. Occasionally individuals will have a CXR or CT scan for another clinical investigation in which lung cancer is noted as an unexpected finding without any symptoms.

The anticipated clinical pathway with screening is that individuals at risk, variously defined but usually based on age and the number of pack years of smoking, will be offered a LDCT scan. If an abnormality is noted of a specific size/volume, then further confirmatory tests such as repeat CT

scan will be undertaken. Some initially positive tests will be confirmed as early cancer (true positives) and treated as such, but many will be cleared of having lung cancer through additional investigations (false positives) and will have had the additional tests and any associated anxiety, without achieving potential benefit from having a lung cancer identified earlier. There may also be patients who although not having lung cancer, are found to have significant other findings and can be treated successfully, and so may also have benefited from screening through early treatment of these non-lung cancer diseases. For individuals who have no identified abnormalities on the LDCT screen the majority will be true negatives, who truly have no lung cancer at the time of the CT scan. However, there may be occasional individuals who have an early cancer which is overlooked.

4.6 Outcomes

In current practice the main events of importance will be the effect of the lung cancer symptoms, the adverse effects of the investigations (particularly bronchoscopy/biopsy) and treatments (particularly surgery, chemotherapy and radiotherapy), and death. Balancing chances of improved survival with impact on health related quality of life of lung cancer symptoms and adverse events is likely to be the major concern to patient, family and clinician, heightened, given that life expectancy will be measured in months rather than years. Median survival for lung cancer based on data for England and Wales in 2007 was 5 months [18]. This represents a slight increase from 3 months in 1971-2. More recent data for 2013 shows slight further improvement since 2007, with a median survival of approximately 7 months.

In a health system where screening was in place, the key patient events would be the same, although there would be a hope that there would be an improvement in survival of lung cancer patients as more would be identified at an earlier stage, which would make them more amenable to treatment with curative intent. More surgical operations might also be expected too if this were the case. Arguably the number of lung cancer cases would not be expected to change, but overdiagnosis associated with screening is a general concern in any screening programme (see below). In addition to patient events that might be expected in normal care, events associated with screen false positives and negatives also need to be considered if screening is in place, and in this respect the effects on patients of additional investigations and associated anxiety arising from false positives are likely to be very important.

This suggests that in terms of comparing whether a system with and without screening for lung cancer the most important outcomes to help determine effectiveness and cost-effectiveness would be:

- Mortality/survival from lung cancer
- Stage of the lung cancers
- Number of lung cancers
- All-cause mortality
- Health related quality of life (including effect of being a false positive)
- Numbers of true positives/false positives/false negatives/true negatives relative to final determination based on full investigation and clinical follow-up

Other important outcome information would include:

- Indeterminate results

- Number of initial scans and follow-up investigations
- Radiation dose of screening and follow-up CT scans
- Number and type of treatments
- Complications and adverse events
- Associated costs of all outcomes

Alongside outcomes, criteria which need to be met have been designed to help make decisions on whether screening programme should be implemented. Wilson and Junger developed the original criteria but these have evolved further [19]. The NSC criteria are the ones which are most relevant for this report. The Criteria for appraising the viability, effectiveness and appropriateness of a screening programme are provided in Appendix 1, but briefly cover aspects of the condition, the test, the intervention, the screening programme and the implementation criteria [20].

Specifically for the screening programme the following criteria are suggested:

- There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (such as Down's syndrome or cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.
- There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public.
- The benefit gained by individuals from the screening programme should outweigh any harms for example from overdiagnosis, overtreatment, false positives, false reassurance, uncertain findings and complications.
- The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (value for money). Assessment against this criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource.

There are also several special issues which need to be considered in the general evaluation of a screening test, arising from insight from the evaluation of existing population screening programmes such as mammography for breast cancer [16].

- Overdiagnosis bias: small, slow-growing lesions are detected by screening that would never become symptomatic within a patient's lifetime in the absence of screening
- Length bias: screening introduces a bias in relation to expected survival by detecting more patients with less aggressive disease (who have longer survival) and fewer of those with more aggressive disease, because the duration of asymptomatic disease is longer in less aggressive tumours
- Lead-time bias: screening-detected patients are accorded extended survival times solely because cancer was detected earlier owing to screening, although death occurred at the

same time as would have happened without screening (i.e. the intervention yields no benefit).

4.7 Evidence and existing guidance

4.7.1 Last NSC guidance

The current UK NSC guidance was formulated in 2006 and is that a systematic population screening programme is not recommended for lung cancer screening (including with LDCT scanning) in adult cigarette smokers. This was reinforced by a covering note in 2007. There is a note that the policy will be reviewed again after the results of the NELSON randomised lung cancer screening trial are published [21].

The main evidence base for the current policy is a health technology assessment by Aberdeen Health Technology Assessment Group in 2006 [16] [22]. Based on systematic reviews they concluded that there was virtually no directly relevant RCT evidence, and that such evidence demonstrating impact on mortality was essential before concluding that screening for lung cancer with LDCT was effective. The report ended with a summary of the degree to which each of the NSC criteria were or were not met at the time of compiling the report. The report also considers the theoretical components of a health economic model.

4.7.2 The National Lung Screening Trial (NLST)

The NLST, an RCT comparing screening with LDCT with CXR was already in progress at the time of the NSC guidance [23]. 53,454 persons at high risk for lung cancer in 33 US medical centres were randomised from August 2002 to April 2004, 26,722 to three annual screenings of LDCT and 26,732 to single-view posteroanterior CXR. All participants were followed to 31/12/2009. The rate of lung cancer deaths was reduced from 309 per 100,000 person years in the radiography group to 247 per 100,000 person years in the LDCT group, a 20.0% reduction (95% CI 6.8 to 26.7). On this basis they concluded that screening with LDCT reduces mortality from lung cancer. A critical assumption in generalising these results to health systems where no screening is currently in place is that screening with CXR has no effect. Evidence for this proposition was taken from the results of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial [24].

4.7.3 U.S. Preventive Services Task Force (USPSTF) Guidance 2013

Like the NSC in 2006, in 2004 the USPSTF found inadequate evidence to recommend for or against screening for lung cancer, including with LDCT. In 2013 this guidance was updated which led to a revised favourable recommendation [25]:

“The USPSTF recommends annual screening for lung cancer with LDCT in adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery.”

The most influential clinical effectiveness evidence was the NLST and the precise screening programme recommended was informed by a modelling study which considered the likely impact of many alternative scenarios in terms of number of lung cancer cases prevented [1]. This however fell

short of a full cost-effectiveness analysis with the choice of optimum scenario by the USPSTF being based on "the screening scenario with a reasonable balance of benefits and harms".

4.7.4 Cochrane Review

In parallel with the USPSTF the Cochrane Collaboration was also updating a systematic review of the available evidence [12]. They identified 9 trials (8 RCTs and 1 controlled trial) but most of these considered comparisons of screening with CXR of different intensities. Only one study investigating the effectiveness of LDCT was included, NSLT, but the review was more cautious about the conclusions indicating:

"Annual LDCT screening is associated with a reduction in lung cancer mortality in high-risk smokers but further data are required on the cost effectiveness of screening and the relative harms and benefits of screening across a range of different risk groups and settings."

4.7.5 Ongoing trials of LDCT

Both the USPSTF and the Cochrane Review noted that there were several on-going European trials, which are particularly important because they offer an opportunity to corroborate the findings of NLST and because they compare LDCT with no screening. Foremost amongst these in terms of size is the Dutch-Belgian randomised lung cancer screening trial, NELSON, with 15,822 participants enrolled beginning in August 2003, 7915 assigned to LDCT with increasing intervals and 7907 to no screening. Although analysis of screening test performance and interval cancers has been performed the results of the primary outcome, lung cancer mortality are still awaited [26]. In the UK context there is also the UKLS, a pilot trial with approximately 4000 participants randomised to CT or no screening which is preparing its final report [27].

4.8 Review objective

To assess the effectiveness and cost-effectiveness of screening for lung cancer with LDCT scanning. It is being undertaken specifically to support a decision by the NSC updating its 2006 guidance, ideally incorporating new evidence on impact on lung cancer mortality from the NELSON RCT.

5 Methods: Evidence syntheses

5.1 Review questions

Research directly relevant to the assessment of the effectiveness and cost-effectiveness of LDCT will be identified and systematically reviewed using the general principles suggested by the NHS Centre for Reviews and Dissemination [28].

The components of underlying review questions will be:

Population: Persons at high risk of lung cancer. We will be inclusive with respect to definition of high risk in order to facilitate exploration of risk as a particular feature by which effectiveness and cost-effectiveness might vary.

Intervention: Screening programme involving LDCT, including both single and multiple rounds. It will be important to carefully define and record variation in the screening programme not only in the techniques used to do the initial screen but also the criteria used to define positive tests and how positive (and indeterminate tests where applicable) are followed up.

Comparator: Although the main comparator of interest will be no screening, comparison of LDCT with other comparators, particularly CXR will also be considered in the context of exploring the possibility of network meta-analysis (see below)

Outcomes (effectiveness review):

- Mortality/survival from lung cancer
- Stage of the lung cancers
- Number of lung cancers
- All-cause mortality
- Health related quality of life
- Numbers of true positives/false positives/false negatives/true negatives relative to final determination based on full investigation and clinical follow-up

Outcomes (cost-effectiveness review):

- Incremental cost-effectiveness ratios
- Costs

Study designs (effectiveness review):

- RCTs

Study designs (cost-effectiveness review)

- Cost-effectiveness/ -utility, /-benefit evaluations
- Health economic models of the above
- NHS relevant costing studies

5.2 Search strategy

As a general principle we will assume that the searches and included studies identified in the 2006 HTA [16] which underpinned the previous NSC guidance and searched up to 5 January 2005, appropriately cover the literature up to that point. For safety we will allow some overlap and conduct our updating search from 1/7/2004. Only if the target of our search was not covered by the 2006 HTA report will we extend searches back to the inception of any databases searched.

The search strategy, which will identify both evidence on effectiveness and cost-effectiveness will comprise the following main elements:

- Searching of electronic databases;
- Contact with experts in the field;
- Scrutiny of bibliographies of retrieved papers (citation chasing);
- Follow-up on mentions of potentially relevant HTAs;
- Checking progress of on-going trials mentioned in key prior systematic reviews

The main electronic databases of interest will be:

- Medline & Medline in Process (OVID)
- Embase (OVID)

- PsycINFO (OVID)
- HMIC (OVID)
- Econlit (EBSCO)
- Cinahl (EBSCO)
- Web of Science (ISI)
- The Cochrane Library (ALL)
- NRR (National Research Register)
- Web of Science Proceedings
- Current Controlled Trials
- Clinical Trials.gov
- FDA website
- EMEA website

These will be searched from 1/7/2004, and will be limited to English Language and human only populations. Study design search filters will be used to identify randomised controlled trials (for effectiveness) and studies reporting costs, economics, utilities and the development of decision models. The searches will be developed and implemented by a trained information specialist (CC) and will be piloted by the review team prior to agreeing the final search syntax. This final syntax will be clinically approved by our clinical experts prior to the searches being run. A sample search strategy used for scoping is included as Appendix 2.

Whilst it is expected that many of the parameters for any economic model (see below) will be derived from the search for the systematic review for clinical and cost-effectiveness, it is expected that additional searches will need to be conducted too. Additional searches may also be required if a network meta-analysis (see below) is thought to be feasible and helpful.

5.3 Review conduct

5.3.1 Inclusion criteria

These will be derived from the stated components of the review questions. Criteria for the initial screening are likely to focus on intervention and study design. The inclusion criteria will be piloted before full implementation.

5.3.2 Exclusion criteria

Studies will be excluded if they do not match the inclusion criteria. In addition certain studies will not be considered, particularly:

- Animal models
- Preclinical and biological studies
- Non-systematic reviews, editorials, opinions
- Non-English language papers, without an English abstract
- Reports published as meeting abstracts only, as there are unlikely to be sufficient methodological details to allow critical appraisal of study quality.

5.3.3 Screening

Titles and abstracts will initially be examined for inclusion by two reviewers independently and disagreement resolved by consensus, with inclusion as the default in case of continuing

disagreement. The full text of potentially relevant studies on title and abstract will then be further examined by two reviewers independently and disagreement resolved by consensus, with arbitration by a third reviewer if necessary.

5.3.4 Data extraction strategy

Data will be extracted independently by one reviewer using a standardised data extraction form and checked by another. Disagreements will be resolved by discussion, with involvement of a third reviewer in case of difficulty resolving the disagreement.

5.3.5 Quality assessment strategy

Consideration of study quality will be based on the guidelines set out by the NHS Centre for Reviews and Dissemination and will be adapted according to the nature of included studies being considered.

For RCTs we will use the Cochrane Risk of Bias tool [29].

Economic evaluations will be assessed using the Consensus on Health Economic Checklist (CHEC) questions developed by Evers et al [30] and any studies based on decision models will be assessed against the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines for good practice in decision analytic modelling [31].

Quality will be assessed independently by one reviewer and checked by another, discrepancies again being resolved by discussion, with involvement of a third reviewer if necessary.

5.4 Methods of analysis/synthesis

All data will be tabulated and primarily considered in a narrative review. Where appropriate, meta-analysis will be employed to provide summary estimates of effectiveness, closely taking into account any heterogeneity observed. For any RCT evidence meta-analysis will be carried out using fixed and random effects models, using STATA or equivalent software as required. Heterogeneity will be explored through consideration of the study populations, methods and interventions, by visualisation of results and, in statistical terms, by the χ^2 test for homogeneity and the I^2 statistic.

Meta-analysis will not be appropriate in the review of economic evaluations, models and costing studies. A narrative approach will be adopted.

The potential for network meta-analysis will be considered, incorporating RCT evidence on LDCT screening vs CXR screening and CXR screening vs no screening to inform the comparison of LDCT screening vs no screening, where evidence is currently limited. If appropriate to conduct, the network meta-analysis will be done in WinBUGS following the approaches recommended [32] [33]. Fixed and random effects models will be run, and their convergence and model fit will be assessed. As with the pair-wise meta-analyses, heterogeneity between studies will be explored [34] and the possibility of inconsistency within the network will be investigated [35]. As well as estimating the relative effectiveness of LDCT screening test compared to all other screening tests included in the network, outputs from the network meta-analysis will allow statements to be made on the probability that LDCT screening is more effective than the other screening tests in the network.

6 Methods: Model-based analysis of the effectiveness and cost-effectiveness of screening for LDCT scanning for lung cancer

6.1 Research question

To assess the cost-effectiveness of screening with LDCT scanning for lung cancer relative to no screening.

6.2 Evaluation of costs and cost-effectiveness

The approach, as suggested in the commissioning brief will be to develop a model of cost effectiveness of LDCT screening, using an existing model as a starting point or where an appropriate model does not exist, develop a new health economic model de novo. The decision on whether an appropriate existing model exists will be informed by the systematic review of cost-effectiveness studies (see above).

The question definition would be identical to that already defined above, with the exception that the primary economic model output will be the incremental cost-effectiveness ratio (ICER) where health outcomes are measured in quality-adjusted life-years (QALYs). However, if it becomes apparent that producing ICERs in per QALY terms is not feasible, then ICERs in terms of life-years (LYs), or lung cancers or cancer deaths averted may be reported. These may be reported even if the cost per QALY is feasible to allow comparison with other important recent cost-effectiveness models which express their results as cost per life year gained or cost per lung cancer death avoided.

6.3 Development of the health economic model

The model will be developed in accordance with the current ISPOR guidance for Good Practice in Decision Analytic Modelling [31] and NICE Decision Support Unit Guidance [2].

The exact format of the model will be determined when a fuller picture of the existing models has emerged. Provisionally however a decision-analytic model would seem to be adequate to consider the cost-effectiveness of screening with LDCT relative to no screening where RCT evidence is available to provide direct information on the impact of the screening programme on patient outcomes. Multiple scenario analyses will be employed to investigate whether variation in definition of risk, in terms of age, sex and smoking history, or nature of the screening programme, particularly in terms of length of screening interval and number of rounds, would lead to important variation in cost-effectiveness.

There is no specific reference case for cost-effectiveness models done for NSC, so in lieu of this, and as the model is to specifically investigate the cost-effectiveness in the UK, we will use the NICE reference case as a starting point for considering key features of our approach [36]. For instance, a lifetime horizon will be used in the model and costs and benefits will be discounted at a rate of 3.5%. Our analysis will be from the perspective of the NHS as well as a personal social services perspective as appropriate.

Model parameters will generally be taken from the systematic reviews undertaken as part of the evidence synthesis. Supplemental reviews will need to done to address specific additional parameter requirements for the model. Given that there may be a large number of these, it cannot be guaranteed that these will be systematic reviews [2]. However, if an existing systematic review is

available, that will be used, or if not the approach to the review will as systematic as possible, particularly with respect to documentation of the approach taken.

Costs for the model will be obtained from NHS Reference Costs, the Personal Social Services Research Unit (PSSRU), the British National Formulary (BNF) and any other relevant sources of data identified. Existing trials, particularly the UKLS, can be expected to provide much useful information on resources and costs needed to deliver a screening programme on the UK. Utility values will preferably be obtained from literature or by clinical expert elicitation in the absence of published estimates.

The effect of uncertainty in parameter values upon the cost-effectiveness will be explored through univariate sensitivity analyses, and probabilistic analyses if feasible and potentially informative.

7 Expertise in the team and Advisory Group

Name	Institution	Role/expertise
TAR team		
Prof Chris Hyde	Exeter Test Group, PenTAG and PenCLAHRC, UEMS	Prof of Public Health and Clinical Epidemiology; public health physician; lead for systematic review and project overall lead
Dr Marcela Haasova	PenTAG, UEMS	Research Fellow; systematic reviewer
Dr Helen Coelho	PenTAG, UEMS	Research Fellow; systematic reviewer
Dr Zhivko Zhelev	Exeter Test Group and PenCLAHRC, UEMS	Research Fellow; systematic reviewer
Prof Martin Hoyle	PenTAG, UEMS	Prof of Heath Technology Assessment; economic modelling and overall lead for cost-effectiveness
Ms Nicola Huxley	PenTAG, UEMS	Research Fellow; economic modelling
Dr Tristan Snowsill	PenTAG, UEMS	Research Fellow; economic modelling
Dr Jaime Peters	Exeter Test Group, PenTAG and PenCLAHRC, UEMS	Senior Research Fellow; network meta-analysis
Mr Chris Cooper	ESMI, UEMS	Senior Research Fellow; information science
Mrs Sue Whiffin	ESMI, UEMS	Senior Administrator; project coordinator
Mrs Jenny Lowe	ESMI, UEMS	Administrator; document retrieval
Steering Group		
Dr Kevin Smith	Deputy Director Healthcare Public Health England, Yorkshire and the Humber	Nominee of NSC; public health physician

Prof Carl Roobottom	Prof of Radiology, Radiology Academy, Derriford Hospital, Plymouth	Radiology expert
To be arranged		Chest physician
Prof Willie Hamilton	Professor of Primary Care Diagnostics, UEMS	General practitioner; diagnosis of cancer in primary care
Prof John Field	Professor of Molecular Oncology, University of Liverpool	Clinical Professor of Molecular Oncology; representative of UKLS
Prof Harry de Koning (or other representative of NELSON)	Professor of Evaluation of Screening, Erasmus Medical Centre, Rotterdam	Clinical researcher; representative of NELSON
Renée Manser	Department of Haematology and Medical Oncology, Peter MacCallum Cancer Institute, St Andrew's Place, East Melbourne 3002, Victoria, and Department of Respiratory Medicine, Royal Melbourne Hospital, Melbourne, Australia.	Clinical researcher and chest physician; representative of Cochrane Review Group
Patient representative (to be arranged via PenPIG*)		Patient view
(Suggested member by Kevin Smith to be arranged)		Ethicist
Prof Obi Ukoumunne	Prof of Statistics, University of Exeter Medical School	Statistician
Abbreviations: PenTAG, Peninsula Technology Assessment Group; UEMS, University of Exeter Medical School; ESMI, Evidence Synthesis and Modelling for Improvement in Heath; PenPIG, Peninsula Patient Involvement Group; PenCLAHRC, Peninsula Collaboration for Leadership in Applied Health Research		

8 Competing interests of authors

TAR Team: None

Advisory group members: To be confirmed

9 Timetable/milestones

Event	**Expected due date**
Submit protocol to NIHR	December 2015
Approval of protocol	ca February 2015
Begin HTA *	July 2015

Literature searching and assessment of papers for inclusion in the review	August 2015
Data extraction and quality assessment:	September 2015
Data synthesis	October 2015
Economic modelling	July-October 2015
Draft report for internal and external advisors	November 2015
Full report submitted to NIHR/NSC	December 2015

* Start will be determined by the availability of data from the NELSON study. As soon as we have confirmation from the study authors that a publication is expected within three months, we will commence the HTA. The time intervals of the subsequent steps will then be as indicated in the provisional time-table, taking into account the revised start date.

10 Details of the TAR centre

The Peninsula Technology Assessment Group (PenTAG) is part of the Evidence Synthesis and Modelling for Health Improvement (ESMI) group at the University of Exeter Medical School. PenTAG was established in 2000 and carries out independent Health Technology Assessments for the UK HTA Programme, as well as for other local and national decision-makers. The group is multi-disciplinary and draws on individuals' backgrounds in public health, health services research, computing and decision analysis, systematic reviewing, statistics and health economics. ESMI is made up of discrete but methodologically related research groups, among which Health Technology Assessment is a strong and recurring theme.

Health technology assessment projects include:

- The effectiveness and cost-effectiveness of immunosuppressive therapy for kidney transplantation in adults (review of technology appraisal guidance 85): a systematic review and economic model
- The effectiveness and cost-effectiveness of immunosuppressive therapy for kidney transplantation in children (review of technology appraisal guidance 99): a systematic review and economic model
- Ofatumumab in combination with chlorambucil or bendamustine for previously untreated chronic lymphocytic leukaemia
- Obinutuzumab for previously untreated chronic lymphocytic leukaemia
- The effectiveness and cost-effectiveness of erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating cancer-treatment induced anaemia (including review of TA142): a systematic review and economic model
- Bosutinib for previously treated chronic myeloid leukaemia a single technology appraisal

- Erythropoiesis stimulating agents (epoetin and darbepoetin) for cancer-treatment induced anaemia
- Diagnostic strategies for identifying Lynch syndrome in early-onset colorectal cancer patients
- Sysmex RD-100i OSNA system and Metasin for intraoperative detection of sentinel lymph node metastases in breast cancer

For a full list of previous projects please see http://medicine.exeter.ac.uk/esmi/workstreams/healthtechnologyassessment/

11 Appendices

Appendix 1

NSC Guidance

Criteria for appraising the viability, effectiveness and appropriateness of a screening programme

Updated 23 October 2015

Contents

A.The condition

B.The test

C.The intervention

D.The screening programme

E.Implementation criteria

F.References

A. The condition

1. The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.

2. All the cost-effective primary prevention interventions should have been implemented as far as practicable.

3. If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.

B. The test

4. There should be a simple, safe, precise and validated screening test.

5. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.

6. The test, from sample collection to delivery of results, should be acceptable to the target population.

7. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.

8. If the test is for a particular mutation or set of genetic variants the method for their selection and the means through which these will be kept under review in the programme should be clearly set out.

C. The intervention

9. There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme shouldn't be further considered.

10. There should be agreed evidence based policies covering which individuals should be offered interventions and the appropriate intervention to be offered.

D. The screening programme

11. There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (such as Down's syndrome or cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.

12. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public.

13. The benefit gained by individuals from the screening programme should outweigh any harms for example from overdiagnosis, overtreatment, false positives, false reassurance, uncertain findings and complications.

14. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (value for money). Assessment against this criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource.

E. Implementation criteria

15. Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme.

16. All other options for managing the condition should have been considered (such as improving treatment or providing other services), to ensure that no more cost effective intervention could be introduced or current interventions increased within the resources available.

17. There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.

18. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme.

19. Evidence-based information, explaining the purpose and potential consequences of screening, investigation and preventative intervention or treatment, should be made available to potential participants to assist them in making an informed choice.

20. Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.

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Appendix 2

Sample search strategy

DRAFT SCOPE: MEDLINE ONLY

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

#	Searches	Results
1	exp Lung Neoplasms/	184038
2	((lung$ or bronchial or pulmon$) adj3 (cancer$ or neoplas$ or tumor$ or tumour$ or carcinoma$ or adenocarcinoma$ or small cell)).ti,ab,kw,ot.	159324
3	1 or 2	230262
4	((CT or CAT) adj3 (scan$ or screen$)).ti,ab,kw,ot.	77143
5	((compute$ adj3 tomogra$) and (scan$ or screen$)).ti,ab,kw,ot.	71346
6	tomogram$.ti,ab,kw,ot.	4068
7	Tomography, X-Ray Computed/	305731
8	4 or 5 or 6 or 7	365926
9	((low$ adj3 dose) or LDCT).ti,ab,kw,ot.	99708
10	3 and 8 and 9	997

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