

BMJ Open LUCSO-1 – French pilot study of Lung Cancer Screening with low-dose computed tomography in a smokers population exposed to Occupational lung carcinogens: study protocol

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ABSTRACT

Introduction Guidelines concerning the follow-up of subjects occupationally exposed to lung carcinogens, published in France in 2015, recommended the setting up of a trial of low-dose chest CT lung cancer screening in subjects at high risk of lung cancer.

Objective To evaluate the organisation of low-dose chest CT lung cancer screening in subjects occupationally exposed to lung carcinogens and at high risk of lung cancer.

Methods and analysis This trial will be conducted in eight French departments by six specialised reference centres (SRCs) in occupational health. In view of the exploratory nature of this trial, it is proposed to test initially the feasibility and acceptability over the first 2 years in only two SRCs then in four other SRCs to evaluate the organisation. The target population is current or former smokers with more than 30 pack-years (who have quit smoking for less than 15 years), currently or previously exposed to International Agency for Research on Cancer group 1 lung carcinogens, and between the ages of 55 and 74 years. The trial will be conducted in the following steps: (1) identification of subjects by a screening invitation letter; (2) evaluation of occupational exposure to lung carcinogens; (3) evaluation of the lung cancer risk level and verification of eligibility; (4) screening procedure: annual chest CT scans performed by specialised centres and (5) follow-up of CT scan abnormalities.

Ethics and dissemination This protocol study has been approved by the French Committee for the Protection of Persons. The results from this study will be submitted to peer-reviewed journals and reported at suitable national and international meetings.

Trial registration number NCT03562052; Pre-results.

INTRODUCTION

Lung cancer was the most common newly diagnosed cancer in 2012 with 1.8 million new cases worldwide. It is also the leading

Strengths and limitations of this study

- This study will test the feasibility and acceptability of CT lung cancer screening in smoking subjects occupationally exposed to lung carcinogen.
- Target population is subjects at high risk of lung cancer with expected favourable benefit-risk balance according to previous screening programmes in smoking subjects.
- Current smokers will be encouraged to enter a smoking cessation programme and smoking cessation will be evaluated.
- This study will assess the incremental cost-effectiveness ratio of this screening programme.
- Target population is not directly identifiable from databases. All subjects aged 55–74 years need to be invited initially for evaluation of eligibility to the screening programme (according to the level of cumulative smoking and exposure to occupational carcinogens).

cause of cancer death, responsible for approximately one out of every five cancer deaths.¹ In addition to smoking, occupational exposure to carcinogens constitutes another major risk factor for lung cancer. Several carcinogenic agents and exposure situations have been classified as definite carcinogens by the International Agency for Research on Cancer (IARC) (group 1) and associated with an increased lung cancer incidence: asbestos, arsenic and arsenic compounds, benzo(a) pyrene, beryllium and beryllium compounds, bis(chloromethyl) ether and chloromethyl methyl ether, cadmium and cadmium compounds, hexavalent chromium derivatives, diesel engine emissions, sulfur mustard,

coal tar, coal tar pitch, soot, coal gasification and coke production, work in iron and steel foundries, certain nickel derivatives, plutonium-239, radon-222, X-rays and gamma rays and daughter products (work in iron ore mines), crystalline silica, the painting profession, tobacco smoke second hand, talc containing asbestiform fibres, aluminium production using the Söderberg process, the rubber industry and welding fumes.

The National Lung Screening Trial (NLST) (USA)² demonstrated the efficacy of annual chest CT screening in populations of smokers (30 pack-years or more) or former smokers who have quit smoking for less than 15 years, with 30 pack-years or more. Following the NLST publication, guidelines and expert opinions have been published all over the world.^{3–12} The majority of these guidelines recommend low-dose chest CT lung cancer screening, but under strictly controlled conditions. In France, in 2014, a task force commissioned by the French National Authority for Health (HAS) conducted a review of the literature on the efficacy, acceptability and safety of low-dose chest CT lung cancer screening and concluded that the level of proof was insufficient to recommend a national lung cancer screening programme, as the benefit-risk balance was unknown.¹³ The most recent review of the literature on lung cancer screening, published in 2016, reached a similar conclusion that the benefit-risk balance of low-dose chest CT screening has not been correctly documented.¹⁴ This benefit-risk balance can be improved in various ways, especially by decreasing the number of false-positives and by optimising the selection of subjects likely to benefit from screening. The benefit-risk balance becomes increasingly more favourable when higher proportions of subjects at high risk of lung cancer are included in screening programmes.^{3–12}

A recent systematic meta-analysis reviewing all cohort studies involving chest CT screening in former asbestos-exposed workers showed that chest CT-based lung cancer detection rates among asbestos-exposed workers were at least equal to the prevalence observed in heavy smokers.¹⁵ CT screening in asbestos-exposed workers appears effective to detect asymptomatic lung cancer and identifies a proportion of stage I cancers similar to that detected in smokers. The authors concluded that CT screening of asbestos-exposed workers could decrease mortality to a similar degree to that observed in heavy smokers and should therefore not be neglected, particularly in individuals co-exposed to tobacco.

In 2015, French national guidelines recommended an experiment of low-dose chest CT lung cancer screening in subjects currently or previously occupationally exposed to lung carcinogens (expert consensus). Based on a review of the literature, this recommendation defined a target population in which the level of lung cancer risk was at least equivalent to or greater than that of the NLST trial population.¹⁶

We present the protocol of this study in this paper.

OBJECTIVES

The primary objective was to evaluate the organisation of low-dose chest CT lung cancer screening in subjects currently or previously occupationally exposed to lung carcinogens.

The secondary objectives were

- ▶ To describe the population recruited in each step of the protocol.
- ▶ To develop a tool to identify subjects exposed to pulmonary carcinogens and with high risk of lung cancer.

To evaluate the impact of the proposed screening programme on smoking cessation at 1, 2 and 3 years.

On the population of workers who were identified as being at high risk of lung cancer and for whom low-dose chest CT lung cancer screening is available:

- ▶ To evaluate the medical impact of low-dose chest CT scan.
 - Measurement of medical irradiation induced by the screening programme (CT dose delivery at screening and of additional radiological interventions).
- ▶ To evaluate the social impact of the screening programme.
 - Description of the medical and health insurance formalities completed at the time of screening: occupational disease notification, submission of a compensation application to the *Fonds d'Indemnisation des Victimes de l'Amiante* (FIVA) (French Asbestos Compensation Fund). These medical and health insurance formalities will concern lung cancers detected by screening and also benign asbestos-related pleural or pulmonary diseases (particularly pleural plaques which are the most common disease after asbestos exposure).
- ▶ To conduct a cost-effectiveness analysis of the programme.

METHODS AND ANALYSIS

The study is a multidepartment, prospective, descriptive study, organised into six work packages (WP) (figure 1):

- ▶ WP1: Methodology—epidemiology.
- ▶ WP2: Evaluation of occupational exposure.
- ▶ WP3: Imaging.
- ▶ WP4: Lung cancer follow-up strategy.
- ▶ WP5: Smoking cessation.
- ▶ WP6: Medical consumption analysis.

Six specialised reference centres (SRCs) in four different regions will recruit about 200–600 eligible subjects per year and per region.

Each of these centres possesses the four essential prerequisites: an occupational health clinic, radiology team with specific chest imaging skills, pulmonology team or network of pulmonologists specialised in lung cancer and smoking cessation team.

In view of the complexity of this organisation, it is proposed to test initially the feasibility and acceptability of the screening programme sequentially for the first 2 years in two SRCs and to extend the study to the other

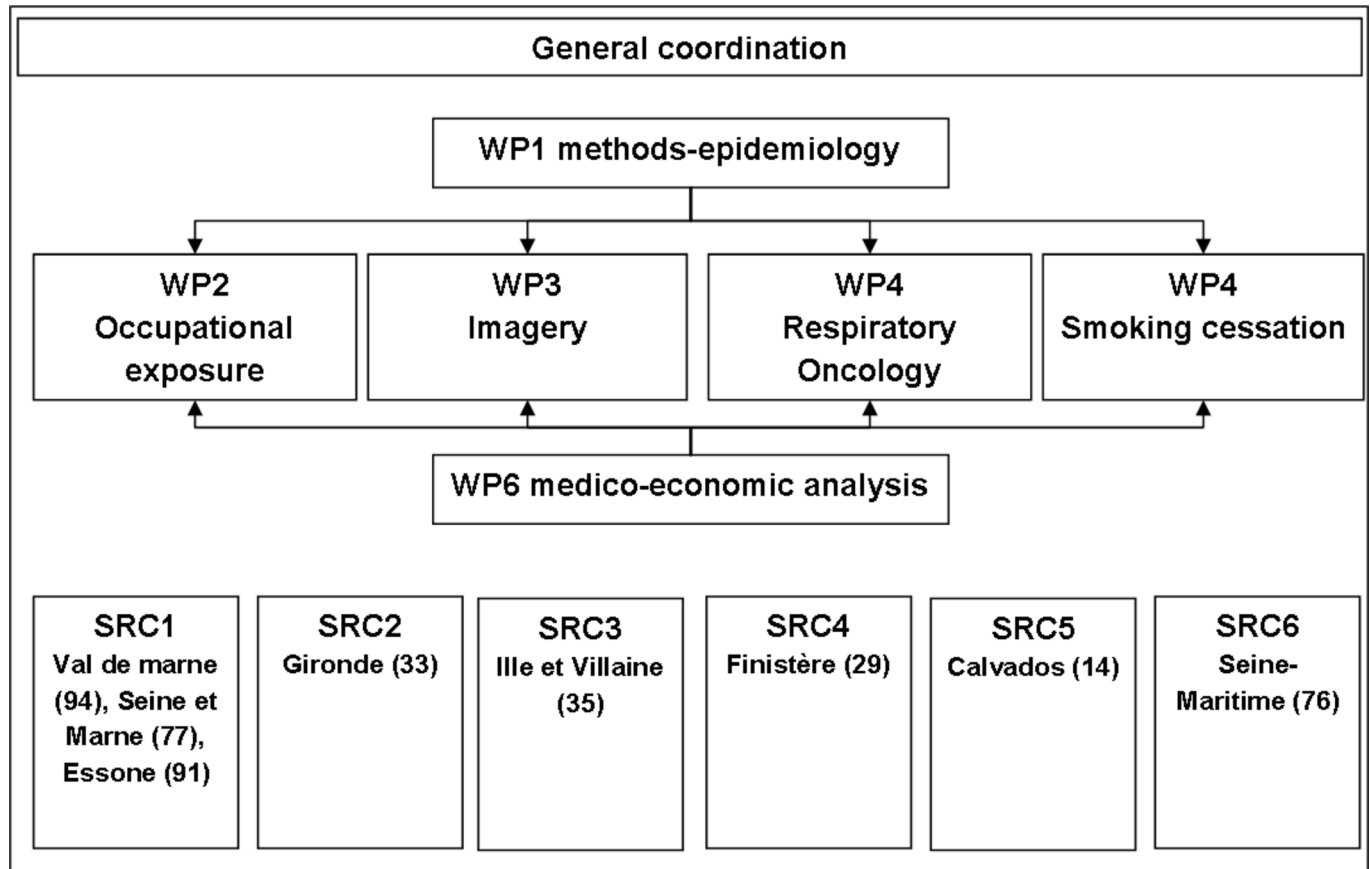


Figure 1 Work packages (WP) and specialised reference centre (SRC) organisation for the LUCSO.

SRCs after 2 years (figure 2). The feasibility will be evaluated by the rate of detected lung cancer and the proportion of lung cancer detected with the chest CT scan programme in subjects exposed to occupational carcinogens. The acceptability will be evaluated by the proportion of subjects undergoing repeated low-dose chest CT screening among eligible responders during the first phase of the study (the first 2 years).

In these two departments, the population aged between 55 and 74 years was estimated to be about 500 000 in 2015 by the French statistics institute (INSEE). Ad hoc adjustments will be decided for the creation of SRCs in the third year on the basis of the data acquired in the two pilot departments, especially on the expected target population participation rate.

Eligibility criteria

Inclusion criteria: Subjects at high risk of lung cancer, as defined in the occupational health surveillance guidelines for subjects currently or previously exposed to lung carcinogens based on an expert consensus (table 1).

Exclusion criteria are the presence of clinical signs of lung cancer, subjects with a history of lung cancer, presence of serious short-term life-threatening comorbidities, absence of occupational exposure to lung carcinogens according to the predefined criteria, subjects already included in another prospective cohort study, subjects already assessed by chest CT scan during the previous

year, no tobacco exposure or insufficient tobacco exposure (<10, <20 or <30 pack-years according to the level of cumulative exposure to different occupational carcinogens as stated in table 1) or smoking cessation for more than 15 years.

Study procedure

Study procedure is described in figure 3.

Step 1: Identification of subjects currently or previously occupationally exposed to lung carcinogens

All healthcare actors of a targeted geographical territory (general practitioners, occupational health physicians, pulmonologists, radiologists and health insurance funds) and concerned by the study will receive detailed information about setting up of the project. Workers' representatives and patients' associations will also be informed about setting up of the project.

In a given department, screening invitation letters will be sent by the cancer screening centre to subjects between the ages of 55 and 74 years by monthly waves over a 2-year period from September 2018.

The invitation letter will comprise an information sheet describing the lung cancer screening eligibility criteria and a simplified, two-page, self-administered questionnaire (AQ1) including questions about all previous jobs during complete working life (professional calendar) and exposure to non-occupational risk factors, especially

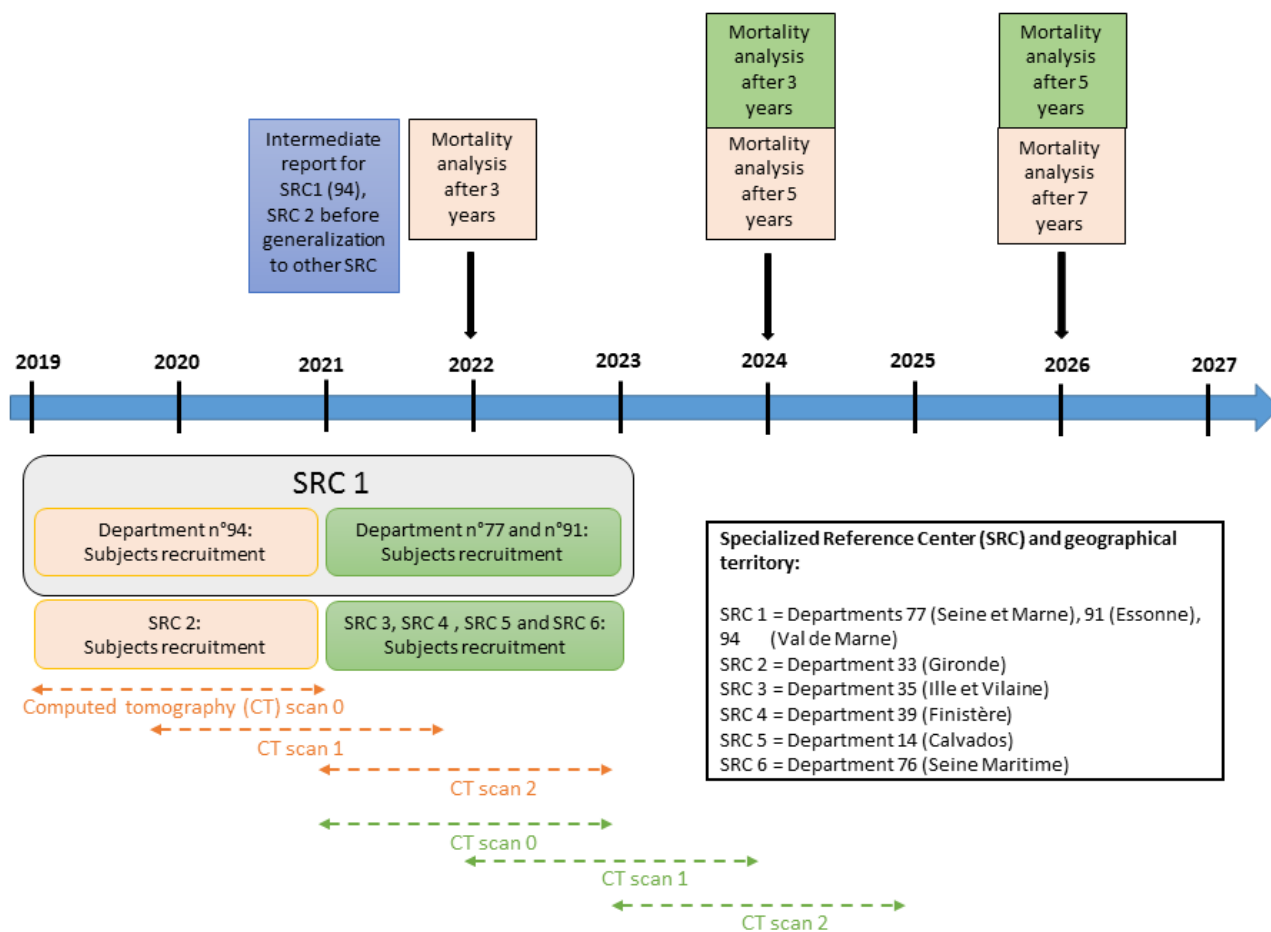


Figure 2 Project phases: recruitment and follow-up calendar.

smoking. This questionnaire will be returned to each SRC and analysed by a clinical research associate (CRA) and, if necessary, by an industrial hygienist. A letter will be sent to ineligible subjects to explain that lung cancer screening is not recommended in their case. Subjects presenting a high probability of occupational exposure to lung carcinogens will be invited to attend the occupational health clinic. Subjects reporting uncertain exposure to lung carcinogens will be asked to fill in and return a more detailed personalised self-administered questionnaire (AQ2) to each SRC.

Step 2: Evaluation of occupational exposure

After evaluation of occupational exposure from AQ2, subjects with high probability of occupational exposure will be invited to the occupational health clinic. A letter will be sent to subjects considered to be ineligible for screening, informing them that lung cancer screening is not recommended in their case. A smoking cessation consultation will be proposed to the subjects contacted, when appropriate.

Step 3: Evaluation of the lung cancer risk level and verification of eligibility

As shown in table 1, subjects will be classified into the following groups:

- Ineligible for screening (insufficient cumulative exposure to occupational carcinogens, insufficient cumulative smoking and/or presence of exclusion criteria). A letter will be sent to the attending physician or to the occupational health physician indicating the most appropriate procedure.
 - Smokers must be encouraged to enter a smoking cessation programme
 - Postemployment or postexposure surveillance of asbestos-exposed workers must be conducted according to French recommendations.¹⁷
 - Prevention procedures for subjects still at work, especially when potentially persistent carcinogen exposure is identified.

All ineligible subjects will be followed up at 1, 2 and 3 years by contacting the general practitioner with the subject's consent in order to collect data on chest imaging, occurrence of lung cancer and smoking status.

Table 1 Definition of subjects at high risk for lung cancer between the ages of 55 and 74 years for a cumulative exposure to occupational pollutant ≥ 10 years

Occupational pollutant	Cumulative level of exposure* or disease	Active or former smoking, after quitting for less than 15 years
Asbestos	Intermediate	≥ 30 PY
	High†	≥ 30 PY
	High‡	≥ 20 PY
	Asbestosis	≥ 20 PY
	Pleural plaques	≥ 30 PY
Other carcinogenic agents§		≥ 30 PY
Co-exposure		
2 carcinogenic agents		≥ 20 PY
≥ 3 carcinogenic agents		≥ 10 PY

Adapted to Delva *et al*¹⁶

Special cases: Crystalline silica (silicosis is necessary to integrate the high-risk group for lung cancer, independently of the duration of exposure); diesel engine exhaust fumes (a high level of exposure defined by employment in underground mines, tunnel construction or underground mine maintenance is necessary to integrate the high-risk group for BPC).

Intermediate exposure: All other documented significant occupational exposure situations. The majority of these situations involve intervention on materials or equipment likely to discharge asbestos fibres.

*From the definition of the jury of the 1999 French consensus conference on the follow-up of asbestos-exposed workers: High exposure: Confirmed, high and continued exposure for a duration equal to or in excess of 1 year; examples: working in the manufacture or transformation of materials including asbestos and their equivalents during intervention on materials or equipment likely to discharge asbestos fibres (eg.: fireproofing, naval construction); Confirmed, high and discontinued exposure of a duration equal to or in excess of 10 years (eg.: mechanics/machine operators on heavy goods vehicle brake systems, cutting of asbestos cement).

†Cumulative exposure duration <5 years.

‡Cumulative exposure duration ≥ 5 years.

§Aluminium production, coal gasification, coal tar pitch, coke production, X-rays and gamma rays, radon, iron ore mines, plutonium, steel foundries, the painting profession, rubber production, chromium(VI) compounds, beryllium, cadmium and its compounds, bis(chloromethyl) ether, chloromethyl methyl ether, metal cobalt with tungsten carbide and welding fumes.

Step 4: Screening procedure

Eligible subjects will receive detailed information, especially concerning the risk of detecting abnormalities on CT scan, overdiagnosis and the risks of radiation exposure.

Active smokers will be encouraged to enter a smoking cessation programme.

Pulmonary function tests will be performed at inclusion. Low-dose chest CT scan will be performed at inclusion, then annually for 2 years (ie, T0, T1, T2). Chest

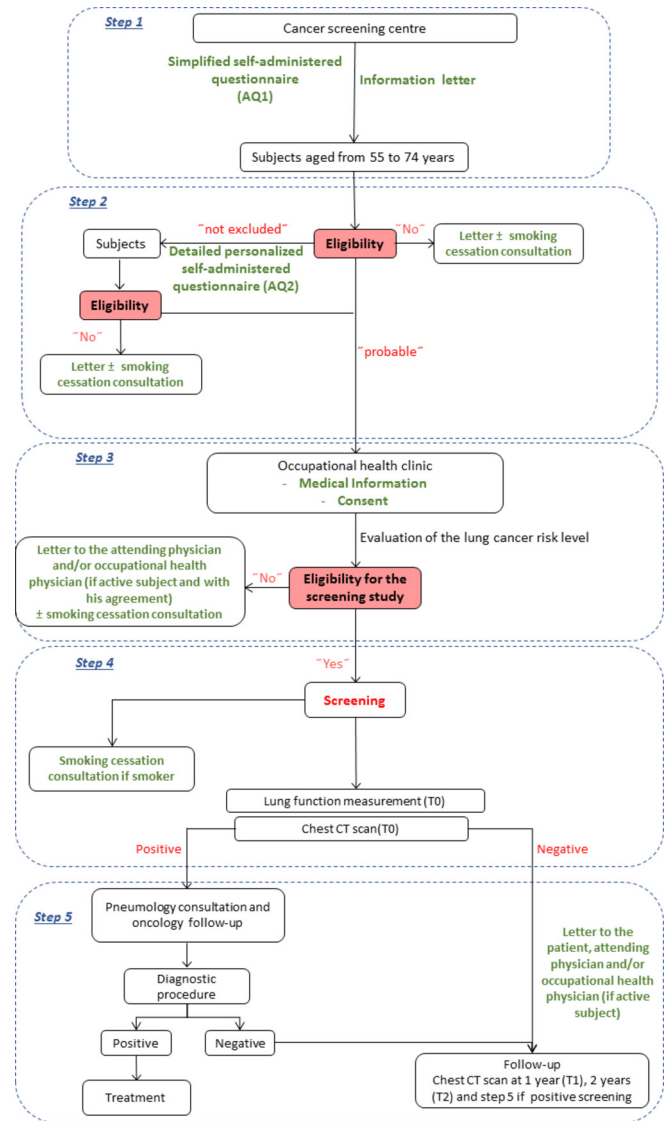


Figure 3 Organisation of lung cancer screening in subjects at high risk of lung cancer in France.

CT scans will be performed with the Maximum Intensity Projection (MIP) reconstruction images and the implementation of a computer-aided detection software by radiologists specialised in chest imaging according to the technical conditions and interpretation guidelines established by the coordinating centre (see online supplementary file 1). The use of additional methods, such as a computer-assisted detection (CAD) system, will be left to the discretion of each centre.

Step 5: Lung cancer follow-up strategy

Only nodules and masses detected on CT screening will be considered to be positive findings. Lesions will be classified according to the British thoracic society guidelines¹⁸ and patients managed according to the European paper recommendations.¹⁹ Subjects presenting other radiological abnormalities on CT should be referred for specific management (particularly benign asbestos-related pleural abnormalities, which may be eligible for specific workers' compensation in France). The proposed diagnostic and

treatment options are presented in online supplementary file 2 .

Smoking cessation (WP5)

In the context of this protocol, subjects referred for smoking cessation will be evaluated and managed according to the *HAS* guidelines revised in October 2014.²⁰ At least, the following parameters will be recorded:

- ▶ Smoking history (especially age of first cigarette and age of daily smoking).
- ▶ Number of cigarettes per day.
- ▶ Cumulative exposure expressed as the number of pack-years.
- ▶ Nicotine dependence by the simplified two-question Fagerström test and determination of carbon monoxide (CO) in expired air.
- ▶ The smoker's motivation to quit smoking.
- ▶ Comorbid anxiety and depression by the Hospital Anxiety and Depression scale.²¹
- ▶ Associated co-consumptions (especially alcohol and cannabis).
- ▶ The subject's weight will be recorded at this first visit.

Initial management will be based on motivational interviewing techniques designed to adapt management to the subject's level of motivation and, if necessary, the smoking cessation drug treatments recommended to relieve smoking withdrawal symptoms and prevent relapse.

The subject's smoking status will be investigated at follow-up (abstinence, decreased smoking or status quo). Any difficulties encountered by the subject will be recorded (occasional smoking, cravings). Determination of carbon monoxide in expired air will be used to confirm the smoking status declared by the subject. The efficacy of treatment and its adverse effects will be evaluated. Dose adjustment or change of treatment can be performed when necessary. The subject's weight curve will be recorded.

At the end of the first and subsequent follow-up visits, the subject will be systematically invited to attend another follow-up visit as long as necessary. The same data will be collected at each follow-up visit.

In the context of the present protocol, the subject's smoking status will be investigated at each step of the lung cancer screening programme.

Cost-effectiveness analysis (WP6)

The aim of this WP is to prospectively assess the incremental cost-effectiveness ratio of this screening programme on the basis of real-life data obtained during the project. More specifically, the costs of the programme, the number and stages of lung cancer diagnosed by the programme, the life-years gained and the quality-adjusted life-years will be analysed. Underlying and contributing causes of death recorded on the death certificate will be obtained. The main assumptions for this cost-effectiveness analysis were: screening does not affect the life expectancy of participants in whom lung cancer is not diagnosed. For participants not known to

have died at the end of the programme, we will estimate the beyond-trial life-years on the basis of their age at the date of last news, gender, smoking status and lung cancer stage, using French life tables adjusted for smoking status and stage-specific annual probabilities of dying from lung cancer. Health state utility will be assessed by economic analysis and will be limited to direct costs, with a lifetime horizon, from the social security perspective. This analysis will incorporate 4% discount per year.

Direct costs include: programme costs, costs to assess subject eligibility, organisation costs (data management, subject's invitation, general practitioner information, meetings, etc), costs of smoking cessation interventions, costs of CT scan, costs of lung cancer management, costs of false-positive results.

To assess the possibility of generalising our results, sensitivity analysis will be performed with the following parameters: effectiveness of screening, by varying the rate of lung cancer detected, by varying the rate of lung cancer without screening programme in this high-risk population, early diagnosis (by varying the distribution with screening), median survival by stage, cost of screening organisation, lung cancer management costs, CT screening cost, cost of consultation to assess occupational exposure.

ENDPOINTS

The primary objective of this study is to evaluate the feasibility of a complex screening programme. The primary endpoint for the first 2years will therefore be the 2-year screening coverage rate at the two-pilot SRCs. This screening coverage rate will be determined by the proportion of subjects undergoing low-dose chest CT screening among all eligible subjects. The following procedure quality indicators will be studied: validity of the procedure in terms of response rate and identification of eligible exposed subjects prior to extension of the screening programme.

The main evaluation over the 7-year period will focus on the following indicators:

- ▶ Examination quality indicator: lung cancer detection rate, lung cancer detection rate by stage.
- ▶ Follow-up indicator: proportion of subjects who quit smoking at each step of screening, mortality rate, and among non-screened subjects, but attending the occupational health clinic: mortality rate, lung cancer rate, lung cancer rate.

Other endpoints will also be studied:

- ▶ Impact of the screening campaign
 - Percentage of subjects accepting to participate in the entire screening programme.
 - Percentage of subjects lost to follow-up (1-year, 2-year follow-up, other complementary investigations).
- ▶ Evaluation of occupational exposure and medical-social consequences

- Validity of the self-administered questionnaire (AQ1) and the detailed self-administered questionnaire (AQ2) for evaluation of occupational exposure in the context of this screening programme but only among subjects who will come to occupational health clinic.
- Number of notified cases of occupational disease asking for compensation (for lung cancer or other asbestos-related occupational disease mainly pleural plaques, pleural visceral fibrosis or asbestosis) following results of CT scan.
- ▶ Lung cancer follow-up strategy
 - Proportion of invasive diagnostic procedures (fibroscopy, puncture under scanner, mediastinoscopy and surgery).
 - Proportion of non-invasive diagnostic procedures (CT scan, PET scan).
 - Proportion of serious and non-serious adverse effects related to screening. Serious and non-serious adverse effects are presented in online supplementary file 3.
- ▶ Health economic analysis
- ▶ Study of time intervals
 - Intervals between each step of screening (evaluation of exposure, referral to the occupational health clinic, inclusion, various follow-up examinations).

Calculation of the number of participants

Estimation of the number of subjects likely to be eligible for the study was based on the results of the ICARE study for the single carcinogen, asbestos and for tobacco.²² The number of potentially eligible subjects is 11 000 subjects for the age-groups and levels of exposure concerned by lung cancer screening and for the departments concerned by the study. In the NLST trial, 1.1% of lung cancers were diagnosed by the first screening CT scan in the low-dose chest CT group.² The proposed study will target a population at higher risk of lung cancer, in which a higher rate of lung cancer is expected. Response rate in lung cancer screening is estimated around 30%.²³ If low-dose chest CT scan is performed in 3000 subjects on inclusion in this study, we will be able to demonstrate a significant difference of 0.5% in lung cancer detection rates between this study (1.8%) and the NLST trial (1.1%) with power statistics of 90%.

Impact of the pilot study

This French pilot lung cancer screening programme is designed to test the feasibility of organised lung cancer screening in a population of subjects occupationally exposed to lung carcinogens and tobacco in two departments. Data from this pilot study will be necessary to envisage possible extension to six other departments and then to all of France. The acceptability of the screening programme by the target population constitutes one of the prerequisites for implementation of a nationwide screening programme.²⁴

Patient and public involvement

The development of the research question and outcome measures and the design of the study were developed without patients. However, before patient's inclusion, workers' representatives and patients' associations will be informed about setting up of the project. Information letter on the study results will be sent to participants.

Ethics and dissemination

The research results will be published in peer-reviewed national and international journals and presented at national and international conferences. Data curation will be 10 years.

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Competing interests OB declares competing interest with MSD and Astra-Zeneca. VLD declares competing interest with GSK and Pierre Fabre. Other authors declare that they have no competing interest.

Patient consent for publication Not required.

Ethics approval This protocol study has been approved by the Committee for the Protection of Persons (Authorisation N° 2017–93).

Provenance and peer review Not commissioned; externally peer reviewed.

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