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Detection of pulmonary nodules: comparison of ultra-low dose chest CT and standard low-dose CT. A monocentric, prospective, non-randomized, comparative, open-label study with blind reading of outcomes.

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ABSTRACT

Introduction:

Lung cancer screening in individuals at risk has been recommended by various scientific institutions. One of the main concerns for CT screening is repeated radiation exposure, with the risk of inducing malignancies in healthy individuals. Therefore, lowering the radiation dose is one of the main objectives for radiologists. The aim of this study is to demonstrate that an ultra-low dose (ULD) chest CT protocol, using recently introduced hybrid iterative reconstruction (ASiR-V, GE medical Healthcare, Milwaukee, WI, USA), is as performant as a standard "low dose" (LD) CT to detect non calcified lung nodules ≥ 4mm.

Methods and analysis:

The total number of patients to include is 150. Those are referred for non-enhanced chest CT for detection or follow-up of lung nodule and will undergo an additional unenhanced ULD CT acquisition, the dose of which is on average 10 times lower than the conventional LD acquisition. Total dose of the entire exam (LD + ULD) is lower than the French diagnostic reference level for a chest CT (6.65 milliSievert). ULD CT images will be reconstructed with 50% and 100% ASIR-V, and LD CT with 50%. The 3 sets of images will be read in random order by two pair of radiologists, in a blind test, where patient identification and study outcomes are concealed. Detection rate (sensitivity) is the primary outcome. Secondary outcomes will include concordance of nodule characteristics; inter-observer reproducibility; influence of subjects' characteristics, nodule location, and nodule size; and concordance of emphysema, coronary calcifications evaluated by visual scoring and bronchial alterations between LD and ULD CT. In case of discordance, a third radiologist will arbitrate.

Ethics and dissemination:

The study was approved by the relevant ethical committee. Each study participant will sign an informed consent form.

Trial registration number: *Clinicaltrials.gov* NCT03305978

ARTICLE SUMMARY:

STRENGTHS AND LIMITATIONS OF THIS STUDY

- We will evaluate the sensitivity of an ultra-low dose CT, delivering 10 times less radiation than conventional low-dose CT, to detect lung nodules, in a French population of 150 patients referred for lung nodule check-up or follow-up.
- We will use a recently introduced hybrid iterative reconstruction (ASiR-V) and different levels of ASIR-V will be assessed
- Nodules characteristics will be analyzed in particular the diagnosis of intrapulmonary lymph node**,** which is a benign lesion.
- Patients with morbid obesity (BMI>35) will not be included as image quality of ultra-low dose CT is not acceptable for those morphotypes.
- Readers will be aware of the type of CT acquisition (LD and ULD) and reconstruction, because they are easily recognizable due to the different level of image noise.

INTRODUCTION

Lung cancer is the deadliest cancer in the world (1), mainly due to the fact that it is often diagnosed at advanced stages that are not surgically curable. The current challenge is therefore to detect lung cancer at early asymptomatic stages. Risk factors such as smoking and occupational exposure (mainly asbestos, silica, arsenic, chromium, iron, coal, ionising radiation) are well known and enable to define the target population for such programs.

The National Lung Screening Trial (NLST) was the first study to show that a low dose (LD) (average effective dose of 1.5mSv) computed tomography (CT) lung cancer screening reduced specific death by 20% (95% CI, 6.8 to 26.7; P=0.004) as compared with chest X Ray (CXR) screening (single-view posteroanterior) in actual or former smokers (>30 pack years) patients between 55 and 74 years old (2).

Other lung cancer screening studies are still in progress in Europe, such as the NELSON study in Belgium and the Netherlands, the results of which are expected to be reported soon (3)

However, the drawback of using LD CT at such doses (<1.5 millisievert (mSv)) is that even though irradiating less than standard chest CT, the radiation exposure is still on average 10 times higher than a 2 views CXR, and may be a risk for induced malignancies in itself. (4)

In this context, great efforts are currently being made by CT manufacturers to reduce the dose and maintain diagnostic quality. Technologies such as automated exposure control, lower tube current and iterative reconstruction (5), were recently introduced, enabling further dose decrease for chest CTs, and the concept of “ultra-low dose (ULD) CT” (or submillisievert CT), which delivers a radiation dose approaching that of 2 CXR views at the cost of a slight deterioration of the image quality (6) . Among these technological advances, the most significant is probably the new iterative reconstruction whether full iterative or hybrid. (7,8,9,10)

Promising results have been published for lung nodule detection with ULD CT (11,12,13). However, these studies were conducted on Asian populations, which may have different morphotypes compared to Caucasian populations.

Huber and al. performed a phantom study comparing standard, LD and ULD CT for detection of pulmonary nodules. When compared to standard CT, the detection rate was 95.5% for LD CT (1.76 mSv), and 93.3% for ULD CT (0.13mSv), increasing at 97.5% when adding computer aided diagnosis and maximal intensity projection (14).

Since we started to design our study protocol, Messerli and al. published a study including 202 patients referred for any clinically indicated chest CT. 91.2% nodules were detected using ULD CT (0.13+/-0.01mSv) as compared to LD CT (1.8 ± 0.7 mSv). Sensitivity was significantly higher for larger nodule diameter, lower BMI patients, lower image noise and for solid and calcified nodules (15).

Neroladaki and al. showed the same number of detected nodules between an ULD acquisition (0.16±0.006mSv) with iterative reconstruction and a standard dose filtered back projection acquisition (11.2±2.7mSv), and more nodules detected with model based iterative reconstruction (MBIR) than adaptive statistical iterative reconstruction (ASIR) (16). MBIR is known to better minimize image noise compared to ASIR : Ichikawa and al found a significantly lower image noise with LD (1.6 ± 0.8 mSv) MBIR CT (11.6 ± 1.0 Hounsfield units (HU)) than with LD ASIR CT (21.1 ± 2.6 HU, $p < 0.0005$), a slightly better image quality score for decreased lung attenuation lesion, and no difference in image quality scores for consolidation or mass, ground-glass attenuation, or reticular opacity with MBIR compared to ASIR LD CT (8). But MBIR may slightly deteriorate lesion margin (9), and significantly increases reconstruction time, taking more than 30 minutes, when patients lie less than 10 minutes in the machine. ASIR-V is the latest generation of hybrid iterative reconstruction (GE medical Healthcare, Milwaukee, WI). It combines ASIR and MBIR and enables a better noise reduction than ASIR, with a processing time of only few minutes, suitable to a routine chest CT session (17).

According to the ALARA (as low as reasonably achievable) principle, we hope to validate our ULD chest CT protocol (<0.2mSv), the dose of which is 10 times lower than a usual LD CT, as a

sensitive tool to detect lung nodules. Thus, this ULD CT acquisition could be generalized for lung nodules detection and would consolidate the setup of lung cancer screening programs. Also, this would allow the generalization of ULD protocols, for radiation sensitive populations (children and young adults in particular).

METHODS AND ANALYSIS

Study design and objectives

The objectives of this study are to evaluate the performance of ULD CT for the detection of lung nodules, and the evaluation of nodule characteristics in comparison to LD CT. Furthermore**,** as smoking is a common risk factor, performance for the detection of cardiac and respiratory associated diseases (bronchial abnormalities, emphysema, coronary calcifications) is also evaluated.

An additional ULD CT is performed in patients referred for non-enhanced chest CT for lung nodules check-up or follow-up. The dose delivered with both acquisitions is still lower than the French diagnostic reference level (6.65mSv). We chose to only include nodules ≥ 4mm as the incidence of cancer is very low below this threshold, and are not currently considered as clinically significant (18). A 4 mm threshold was also used for the NLST study (2). In addition, fully calcified nodules are excluded from the analysis because they are constantly benign and easily detected.

We will study nodule subtypes (solid, part-solid and pure ground-glass) and size. Furthermore we will evaluate the performance of ULD CT to diagnose intrapulmonary lymph nodes, which are benign nodules not needing follow up (19), and were not analyzed in previous ULD CT studies.

This trial sponsored by the Grenoble-Alpes University Hospital (CHUGA, France) is designed as a monocentric, prospective, non-randomized study in which the patient is his own control. All outcomes are evaluated by blinded double reading. Patient enrollment started in October 2017 and is expected to be completed in September 2018. Figure 1 summarizes the process of inclusion, intervention and reading, described in detail below.

Primary outcome

Detection rate (sensitivity) of lung nodules in ULD chest CT using the conventional chest LD CT as gold-standard.

Secondary outcomes

1) Diagnostic criteria: true positive (TP), false positive (FP), true negative (TN), false negative (FN), positive predictive value (PPV), negative predictive value (NPV), Specificity (Sp) of ULD CT

2) Concordance of nodule's size, subtype, and diagnosis of typical intrapulmonary lymph node among lung nodules between ULD and LD CT

3) Inter-observer reproducibility for size, subtype and diagnosis of lung nodules in ULD CT

4) Influence of subjects characteristics (age, sex, BMI), nodule location, and nodule size on lung nodule detection with ULD CT

5) Concordance of emphysema detection, type and distribution between ULD and LD CT

6) Concordance of Weston score of coronary calcifications between ULD and LD CT

7) Concordance of visual assessment of bronchial thickening, mucoid impaction or dilatation between ULD and LD CT

Eligibility Criteria

Inclusion criteria

- aged 18 years or older
- referred for non-enhanced chest CT for the following indications:
    - lung nodule check-up or follow-up
    - nodular abnormality on chest X ray
    - morphologic assessment of chronic obstructive pulmonary disease (COPD) or emphysema
    - asbestos exposure
    - assessment before lung radio frequency ablation

- assessment of disease extent of an extra thoracic cancer (in case of iodinated intravenous contrast agent contraindication)
- Check-up before extra-thoracic transplantation (in case of iodinated intravenous contrast agent contraindication).

Exclusion criteria

- Inability to lie down and stay still during the examination
- Inability to hold breath for more than 5 seconds
- Pneumonia in the last 3 months
- Body mass index (BMI) more than 35kg/m²
- Pregnant or breastfeeding women

CT scan acquisitions and reconstructions

The LD and ULD acquisitions are performed on the Revolution CT scanner (GE medical Healthcare, Milwaukee, WI, USA) equipped with the third generation ASIR-V iterative reconstruction. Acquisitions are performed successively in the same CT exam, in the supine position and at suspended full inspiration. Both acquisitions cover the same pulmonary fields from the apex to the costo-diaphragmatic angle, determined on the scout views (2 views).

The LD acquisition is the reference exam for the diagnosis of pulmonary nodules. The acquisition parameters are: spiral CT scanning; 120kVp; automatic modulation of 3D radiation dose ("Smart mA"+ Organ Dose Modulation) with lower bound 100mA, maximal bound 200mA and noise index 10; rotation time: 0.35sec ; modulation 35-70 mAs; pitch = 0.992 :1 and collimation: 80mm. The radiation dose, CTDIvol (volume CT dose index) and DLP (Dose Length Product = CTDIvol x length of exposure) may vary depending on patient attenuation and length of the acquisition. The expected DLP is between 70 and 200mGy.cm (0.98mSv to 2.8mSv) (the effective dose is calculated

by multiplying DLP by a thoracic conversion factor of 0.014 (20)), for an average DLP of 100mGy.cm.

The ULD CT acquisition parameters are: spiral CT scanning; 120kVp; fixed tube current of 10mA; rotation time: 0.35s; 3.5 mAs; pitch: 0.992 :1, collimation: 80mm. These parameters are fixed for all patients. The CTDIvol is constant at 0.24mGy. The DLP will depend only on the length of the acquired chest, different for each patient, expected around 10mGy.cm (0.14mSv). The modulation of the mA is deactivated to allow a very low tube current and therefore an ULD acquisition. The ULD acquisition increases the exam time by up to two minutes.

The reconstruction parameters are identical for both acquisitions: slice thickness: 1.25mm; standard filter and lung filter; contiguous 8-mm thickness Maximal Intensity projection (MIP) reconstruction, and iterative reconstruction with different percentages. We use ASIR-V in our study which is the latest generation of iterative reconstruction techniques. It blends hybrid iterative reconstruction and standard filtered back projection. The percentage of ASIR-V represents the amount of iterative reconstruction, from 0% (filtered back projection only) to 100% iterative reconstruction, which modifies image noise and texture. When designing our study, ASIR-V was not yet studied for chest CT. The CT vendor engineers suggested an empirical percentage between 40 up to 100%, depending on radiologist practice and preferences. We decided to test percentages of iterative reconstruction of 50% and 100%. The LD CT images are reconstructed with 50% ASIR-V (LD) and the ULD CT images with 50% (ULD50) and 100% (ULD100) ASIR-V.

The statistical analyses will be performed twice: with ULD50 and ULD100.

Concerning the additional radiation for included patients, our ULD CT protocol has an expected effective dose between 0.10 and 0.20 mSv, which is about 6 to 20 times lower than the LD protocol (which is the usual dose in our institution for this indication), similar to a 2-views CXR, and to 30 days of natural radiation (21). Moreover, total dose of the entire exam (around 1.1 to 3 mSv) is lower than French diagnostic reference level of 6.65mSv.

Recruitment and intervention

Patients included in the study are those referred for a diagnostic chest CT without contrast media injection. On the day of the CT scan, a radiologist checks the eligibility criteria for the study, and informs the patient who signs a participation consent form if he accepts to join the study. The radiologist then collects the following parameters: height, weight, history of oncology, cardio-respiratory pathology and exposure to smoking. The patient then undergoes the standard diagnostic LD CT acquisition followed by the ULD acquisition. If, however, the dose of the LD acquisition is greater than 6.65mSv, the ULD acquisition is not performed and the patient is excluded from the data analysis. The patient's participation in the study is completed once he leaves the examination room.

The CT images of the LD acquisition are analysed by the radiologist who gives his medical report for the patient's medical management. If the number of nodules ≥ 4 mm identified on this acquisition is ≥6 in one lung, the patient will be excluded from the data analysis because the analysis of the outcomes will be too complicated to implement.

Patient and Public Involvement

Patients or public were not directly involved in the development of the research question. However, lowering the radiation dose is a rising concern for the patients and for public health. Patients were also not directly involved in the design, the recruitment and the conduct of this study.

As a regular medical care, the report of the diagnostic LD CT is sent to the prescribing physician, and to the patients at their request. According to French law, patients will be informed of the global results of the study at their request.

Blind reading of outcomes

For LD, ULD50 and ULD100 reconstructions, 2 radiologists will independently read all the radiological parameters. In order to limit the number of exams assessed by each reader, 4

radiologists split into 2 pairs will participate in the blind reading. Each pair of radiologists (1 junior and 1 senior radiologist) reads the three sets of images for the same patient in a random order.

The term “blind” means that radiologists have neither knowledge of the patient's identity nor access to the results of diagnostic reading. To avoid patient identification, CT acquisitions are anonymized by deleting in the DICOM fields: the name, age and date of birth of the patient; the date and time of the examination and the name of the referring radiologist for the diagnosis. Each patient reconstruction is identified by a random number that differs for each of the two readers. Radiologists never read two series of the same patient consecutively.

Anonymized exams are periodically transmitted to a pair with at least 15 LD, 15 ULD50 and 15 ULD100 reconstructions. The three patient reconstructions are not necessarily given the same day to both radiologists. In addition, the order of presentation is not identical for the two radiologists.

The reading is performed on a diagnostic console (IMPAX software, 6.5.5.3502) (Agfa, Belgium) using Barco MDNC-3121monitors (Barco, Courtrai, Belgium) and includes mediastinal and parenchymal filter reconstructions for each acquisition. The radiologist is free to adapt the level and width of the window to its reading practice (initial parenchymal window defined by a width of 1500UH and a level of -600UH), and to perform multiplanar reconstructions in the different plans of space. The reading also includes the additional MIP reconstruction for each acquisition, in order to sensitize the detection of nodules (22) (this type of reading from MIP series is performed in clinical routine).

Radiologists identify nodules of longer diameter ≥4mm by locating them with the slice number and the lobe. It is known that each lung has three lobes (right upper lobe, middle lobe, right lower lobe, culmen, lingula, and left lower lobe). Each radiologist completes a reading grid for each reconstruction.

The completed grids are given to a Clinical Research Assistant for data entry and identification of discrepancies in identification of nodules between the two radiologists.

We consider that a nodule is the same between the two readers if:

- it is located in the same lobe
- the slice number is identical at ± 5 slices (a nodule will be visible on several successive slices)
- the longest diameter of nodule is the same at ± 2mm (23)

If these criteria are not respected or if a radiologist identifies one or more nodules in addition to or less than the second radiologist, a consensus with a third CHUGA senior thoracic radiologist with 27 years of experience is obtained. This third radiologist is not part of the reading pairs. The consensus is made from anonymized reconstructions and the reconstructions of the same patient are not processed successively.

Data monitoring

All data is monitored by Grenoble-Alpes University Hospital (trial sponsor), in order to verify that for every patient enrolled there is a signed consent form and that the inclusion and exclusion criteria are respected. In addition all data collected in the case report form of every enrolled patient are verified.

Sample size

With a 90% power, to have a sensitivity of detection of nodules with the ULD CT to 90% with a confidence interval to ±10%, it would be necessary to analyze 124 nodules. According to a retrospective analysis of patients with indication of pulmonary nodule CT made at CHUGA, out of 420 patients per year with this indication, 210 present pulmonary nodules with a total of about 400 nodules. It should therefore include about 140 patients to have 124 nodules to be analyzed. Considering a 5% potential loss to follow-up or withdrawal of consent, the actual number of subjects to include is 147 in total. To this are added three potential patients who could be secondarily excluded from the study for a number of nodules ≥6 in one of the lungs. The total number of patients to include is 150. The sample size calculations were carried out using R software version 3.1.0 (library MKmisc, function power.diagnostic.test) (24, 25, 26).

Statistical analysis

In this non-randomized study where each patient is his own control, the threshold $p<0.05$ will be taken into account to define the significance of the statistical tests. Analyses will be carried out in accordance with good statistical analysis practices after freezing of the database and will be carried out with the software R (version $\geq 3.1.0$). If the missing data rate of the primary criterion is between 5% and 20%, the missing data for this criterion will be replaced. The replacement of the missing data will be done, either according to a worst-case analysis strategy, by disfavoring the assumption that one seeks to demonstrate, either by a multiple imputation method. In case of multiple imputations, five imputations will be made, using a linear regression model taking into account the following variables: age, sex, BMI, smoking habit.

The normality of the quantitative parameters will be determined by the Shapiro-Wilks test or by graphical verification of the symmetry of the distribution. When the normality of the distribution of such a parameter has been demonstrated, it will be described by its mean and its standard deviation. Otherwise it will be described by its median, the 25th and the 75th percentile. The qualitative parameters will be expressed in number and percentage.

For the main objective, the sensitivity of the ULD CT (compared to the LD CT) for the detection of nodules will be calculated and accompanied by a 95% confidence interval. For secondary objective 1, the number of TP, FP, TN, FN, PPV, NPV and Sp of the ULD CT (compared to LD CT) will be calculated. For secondary objectives 2, 5, 6 and 7, the concordance of the qualitative variables will be evaluated using the kappa coefficient. The concordance of the quantitative variables will be evaluated using Lin's concordance coefficient. For each coefficient, the 95% confidence interval will be given. For secondary objective 3, inter-observer reproducibility for qualitative variables will be evaluated using the kappa coefficient. It will be evaluated, for the quantitative variables, using the ICC (intra class coefficient). For each coefficient, the 95% confidence interval will be given. For secondary objective 4, a logistic regression model will be implemented. The variable to be explained will be the result of detecting each nodule in ULD CT compared to the LD CT (0 = good

detection / 1 = bad detection). The explanatory variables will be the age, sex and BMI of the patient, the location (lobe) and the size of the nodule. The size of the nodule can be used as a qualitative variable (<5mm, 5-10mm,> 10mm).

An interim analysis including the analysis of the primary endpoint will be performed after inclusion of the first 50 patients. This interim analysis will aim to: decide whether to continue or stop the study for futility and readjust the number of patients if necessary (if the characteristics of the patients included do not correspond to those initially planned (too many patients without nodules ≥4 mm)). In order to maintain an overall threshold of 5% in the final analysis, the interim analysis will be carried out with a threshold of 0.1%. The results of the interim analysis will be taken into account by the steering committee to propose modifications to the analysis plan. For this interim analysis, data from the confrontation between the two radiologists will be used.

Limitations

First limitation of our protocol is that we do not have a true screening population because there is no organized lung cancer screening program in our country yet. Therefore, our study population corresponds to patients routinely referred for lung nodule checkup or follow up instead of a risk-factor based population.

Another limitation is that ULD CT is easily recognizable as the image noise is increased as compared to LD CT, as well as ULD 50 and ULD 100 are possible to distinguish for an experienced radiologist. As a consequence, readers were not blinded for these, but for patient name, sex, age, clinical status, and CT report.

Recall bias is limited by a randomized order of presentation and cutting into several reading sessions.

Although we wanted to have a “western population”, we decided not to include obese patients with a BMI>35, because ULD CT are of poorer quality, due to the need of more radiation-exposure to produce acceptable images. Vardhanabhuti and al. recently found a loss of nodule detection with

iterative reconstructed CT scanners at an effective dose of 0.14±0.01mSv for obese patients with BMI>38 (27).

We decided to test percentage of 50 and 100% of ASIR-V. Tang and al. tested ASIR-V from 10 to 100% in non-enhanced chest and showed ASIR-V has greater potential in reducing image noise and artifacts and maintaining image sharpness when compared to ASIR, and 60% ASIR-V had the highest image quality combining both the objective and subjective evaluation of images (28). This finding, although occurring after the design of our study is close to our chosen 50% level of ASIR-V.

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AUTHOR CONTRIBUTIONS

M. Ludwig is the corresponding author and contributed to the conception of the study, to the inclusion of patients, to the blind reading of outcomes and to the drafting of the manuscript.

E. Chipon contributed to the conception of the study, to the drafting of the manuscript, and is responsible for data management and its integrity.

J. Cohen contributed to the conception of the study, to the inclusion of patients, to the blind reading of outcomes and to the revision of the manuscript.

E. Reymond contributed to the inclusion of patients, to the blind reading of outcomes and to the revision of the manuscript.

M. Medici contributed to the design and application of statistical analysis, and to the drafting of the manuscript.

A. Cole contributed to the blind reading of outcomes and to the revision of the manuscript.

A. Moreau Gaudry contributed to the conception of the study and to the revision of the manuscript.

G R Ferretti is the principal investigator of the study and contributed to the conception of the work, to the inclusion of patients, to the blind consensus of outcomes and to the revision of the manuscript.

All authors approved the final manuscript and agreed to be accountable for all aspects of the work.

COMPETING INTERESTS

The authors declare that they have no competing interests

CONSENT FOR PUBLICATION

Not applicable

ETHICS AND DISSEMINATION

This trial is registered on the ClinicalTrials.gov database (reference NCT03305978) (see supplementary file "trial registration data set"), and was approved by the relevant ethical committee (Comité de Protection des Personnes, CPP sud-est VI, France, 07/07/2017, CPP Reference: AU1342). The Protocol version is N°1.0- Date: May 4th 2017

All patients sign a consent form before being enrolled in the trial, in accordance with the Declaration of Helsinki II.

Once the statistical report is finalized, we plan to publish our results in an international scientific journal and present them in national and international congresses.

DATA STATEMENT

Legal restrictions (French personal data laws) prohibit the authors from making the minimal data set publicly available. These data are available upon request.

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REFERENCES

1. Globocan : Lung Cancer Estimated Incidence, Mortality and Prevalence Worldwide in 2012 http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx)
2. National Lung Screening Trial Research Team, Denise R. Aberle, Amanda M. Adams, Christine D. Berg, William C. Black, Jonathan D. Clapp, Richard M. Fagerstrom, et al. "Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening." *The New England Journal of Medicine* 365, no. 5 (August 4, 2011): 395–409. doi:10.1056/NEJMoa1102873
3. Yousaf-Khan U, van der Aalst C, de Jong PA, et al."Final screening round of the NELSON lung cancer screening trial: the effect of a 2.5-year screening interval." Thorax 2017;72:48-56. 10.1136/thoraxjnl-2016-208655
4. Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation and National Research Council. Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2.Washington, D.C: The National Academies Press; 2006
5. Kubo T, Ohno Y, Seo JB, Yamashiro T, Kalender WA, Lee CH, et al. "Securing safe and informative thoracic CT examinations-Progress of radiation dose reduction techniques". Eur J Radiol. 2017 Jan;86:313–9.
6. Kim, Yookyung, Yoon Kyung Kim, Bo Eun Lee, SeokJeong Lee, YonJuRyu, Jin Hwa Lee, and Jung Hyun Chang. "Ultra-Low-Dose CT of the Thorax Using Iterative Reconstruction:

Evaluation of Image Quality and Radiation Dose Reduction." *AJR. American Journal of Roentgenology* 204, no. 6 (June 2015): 1197–1202. doi:10.2214/AJR.14.13629.

7. Vardhanabhuti, Varut, Robert J. Loader, Grant R. Mitchell, Richard D. Riordan, and Carl A. Roobottom. "Image Quality Assessment of Standard- and Low-Dose Chest CT Using Filtered Back Projection, Adaptive Statistical Iterative Reconstruction, and Novel Model-Based Iterative Reconstruction Algorithms." *AJR. American Journal of Roentgenology* 200, no. 3 (March 2013): 545–52. doi:10.2214/AJR.12.9424.
8. Ichikawa, Yasutaka, Kakuya Kitagawa, Naoki Nagasawa, Shuichi Murashima, and Hajime Sakuma. "CT of the Chest with Model-Based, Fully Iterative Reconstruction: Comparison with Adaptive Statistical Iterative Reconstruction." *BMC Medical Imaging* 13 (2013): 27. doi:10.1186/1471-2342-13-27.
9. Padole, Atul, Sarabjeet Singh, Jeanne B. Ackman, Carol Wu, Synho Do, Sarvenaz Pourjabbar, Ranish Deedar Ali Khawaja, et al. "Submillisievert Chest CT with Filtered Back Projection and Iterative Reconstruction Techniques." *AJR. American Journal of Roentgenology* 203, no. 4 (October 2014): 772–81. doi:10.2214/AJR.13.12312.
10. Montet, Xavier, Anne-Lise Hachulla, Angeliki Neroladaki, Frederic Lador, Thierry Rochat, Diomidis Botsikas, and Christoph D. Becker. "Image Quality of Low mA CT Pulmonary Angiography Reconstructed with Model Based Iterative Reconstruction versus Standard CT Pulmonary Angiography Reconstructed with Filtered Back Projection: An Equivalency Trial." *EuropeanRadiology* 25, no. 6 (June 2015): 1665–71. doi:10.1007/s00330-014-3563-5.
11. Yoon, Hyun Jung, Myung Jin Chung, Hye Sun Hwang, Jung Won Moon, and Kyung Soo Lee. "Adaptive Statistical Iterative Reconstruction-Applied Ultra-Low-Dose CT with Radiography-Comparable Radiation Dose: Usefulness for Lung Nodule Detection." *Korean Journal of Radiology* 16, no. 5 (October 2015): 1132–41. doi:10.3348/kjr.2015.16.5.1132

12. Sui, Xin, Felix G. Meinel, Wei Song, Xiaoli Xu, Zixing Wang, Yuyan Wang, Zhengyu Jin, Jiuhong Chen, Rozemarijn Vliegenthart, and U. Joseph Schoepf. "Detection and Size Measurements of Pulmonary Nodules in Ultra-Low-Dose CT with Iterative Reconstruction Compared to Low Dose CT." *European Journal of Radiology* 85, no. 3 (March 2016): 564–70. doi:10.1016/j.ejrad.2015.12.013

13. Nagatani Y, Takahashi M, Murata K, Ikeda M, Yamashiro T, Miyara T, Koyama H, Koyama M, Sato Y, Moriya H, et al "Lung nodule detection performance in five observers on computed tomography (CT) with adaptive iterative dose reduction using three-dimensional processing (AIDR 3D) in a Japanese multicenter study: Comparison between ultra-low-dose CT and low-dose CT by receiver-operating characteristic analysis".*Eur J Radiol. 2015 Jul; 84(7):1401-12. Epub 2015 Apr 2*

14. Huber, Adrian, Julia Landau, Lukas Ebner, Yanik Bütikofer, Lars Leidolt, Barbara Brela, Michelle May, Johannes Heverhagen, and Andreas Christe. "Performance of Ultralow-Dose CT with Iterative Reconstruction in Lung Cancer Screening: Limiting Radiation Exposure to the Equivalent of Conventional Chest X-Ray Imaging." *EuropeanRadiology*, January 26, 2016. doi:10.1007/s00330-015-4192-3

15. Messerli M, Kluckert T, Knitel M, Wälti S, Desbiolles L, Rengier F, et al. "Ultralow dose CT for pulmonary nodule detection with chest x-ray equivalent dose - a prospective intra-individual comparative study". EurRadiol. 2017 Aug;27(8):3290–9.

16. Neroladaki, Angeliki, Diomidis Botsikas, Sana Boudabbous, Christoph D. Becker, and Xavier Montet. "Computed Tomography of the Chest with Model-Based Iterative Reconstruction Using a Radiation Exposure Similar to Chest X-Ray Examination: Preliminary Observations." *EuropeanRadiology* 23, no. 2 (February 2013): 360–66. doi:10.1007/s00330-012-2627-7.

17. De Marco P, Origgi D. "New adaptive statistical iterative reconstruction ASiR-V: Assessment of noise performance in comparison to ASiR". J Appl Clin Med Phys. 2018

Mar;19(2):275-286. doi: 10.1002/acm2.12253. Epub 2018 Jan 24. PubMed PMID: 29363260; PubMed Central PMCID: PMC5849834

18. Gierada DS, Pinsky P, Nath H, Chiles C, Duan F, Aberle DR. "Projected outcomes using different nodule sizes to define a positive CT lung cancer screening examination". J Natl Cancer Inst. 2014;106:dju284.
19. Ahn MI, Gleeson TG, Chan IH et-al. "Perifissural nodules seen at CT screening for lung cancer". Radiology. 2010;254 (3): 949-56. doi:10.1148/radiol.09090031
20. Task Group on Control of Radiation Dose in Computed Tomography. "Managing Patient Dose in Computed Tomography. A Report of the International Commission on Radiological Protection." *Annals of the ICRP* 30, no. 4 (2000): 7–45
21. Exposition de la population française aux rayonnements ionisants liée aux actes de diagnostic médical en 2012. Rapport IRSN PRP-HOM N°2014-6
22. Jankowski, A., T. Martinelli, J. F. Timsit, C. Brambilla, F. Thony, M. Coulomb, and G. Ferretti. "Pulmonary Nodule Detection on MDCT Images: Evaluation of Diagnostic Performance Using Thin Axial Images, Maximum Intensity Projections, and Computer-Assisted Detection." European Radiology 17, no. 12 (December 2007): 3148–56. doi:10.1007/s00330-007-0727-6.
23. Revel MP, Bissery A, Bienvenu M, Aycard L, Lefort C, Frija G. Are two-dimensional CT measurements of small noncalcified pulmonary nodules reliable? Radiology. 2004 May;231(2):453-8. PubMed PMID: 15128990.
24. A. Flahault, M. Cadilhac, and G. Thomas (2005). Sample size calculation should be performed for design accuracy in diagnostic test studies. Journal of ClinicalEpidemiology, 58(8):859-862.
25. H. Chu and S.R. Cole (2007). Sample size calculation using exact methods in diagnostic test studies. Journal of ClinicalEpidemiology, 60(11):1201-1202.

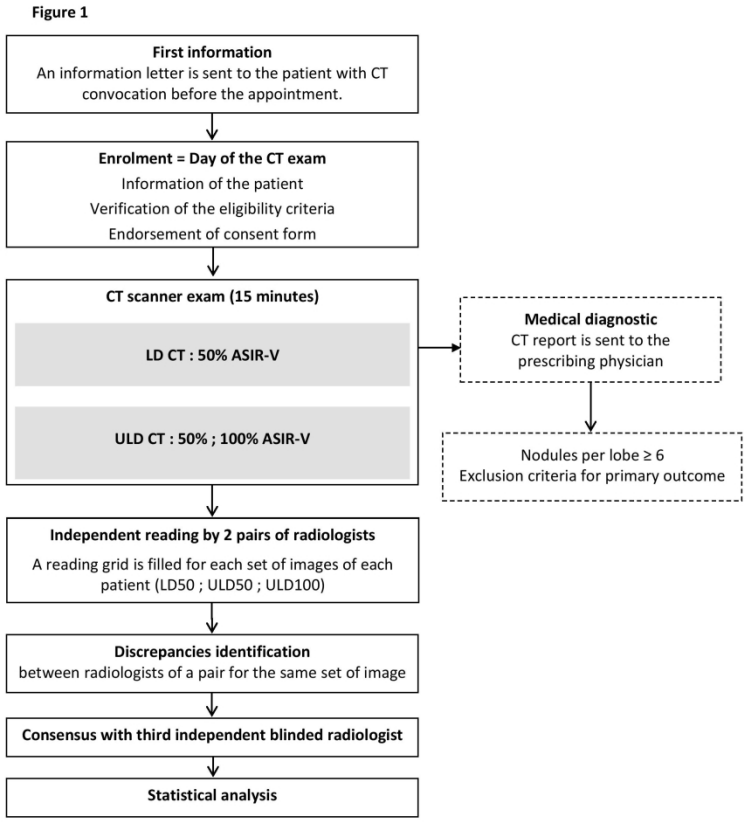
26. M.R. Chernickamd C.Y. Liu (2002). The saw-toothed behavior of power versus sample size and software solutions: single binomial proportion using exact methods. Am Stat, 56:149-155.

27. Vardhanabhuti V, Pang CL, Tenant S, Taylor J, Hyde C, Roobottom C. "Prospective intra-individual comparison of standard dose versus reduced-dose thoracic CT using hybrid and pure iterative reconstruction in a follow-up cohort of pulmonary nodules-Effect of detectability of pulmonary nodules with lowering dose based on nodule size, type and body mass index". Eur J Radiol. 2017 Jun;91:130-141. doi: 10.1016/j.ejrad.2017.04.006

28. Tang H, Yu N, Jia Y, Yu Y, Duan H, Han D, et al. "Assessment of noise reduction potential and image quality improvement of a new generation adaptive statistical iterative reconstruction (ASIR-V) in chest CT". Br J Radiol. 2018 Jan;91(1081):20170521

FIGURE 1 legend:

Study Flow chart. ASIR-V ®, adaptive statistical iterative reconstruction-Véo (GE medical Healthcare, Milwaukee, WI, USA); CT, computed tomography; LD, low dose; LD50, low dose CT with 50% ASIR-V reconstruction; ULD, ultra-low dose; ULD50, ultra-low dose CT with 50% ASIR-V reconstruction, ULD 100, ultra-low dose CT with 100% ASIR-V reconstruction



Study Flow chart. ASIR-V ®, adaptive statistical iterative reconstruction-Véo (GE medical Healthcare, Milwaukee, WI, USA); CT, computed tomography; LD, low dose; LD50, low dose CT with 50% ASIR-V reconstruction; ULD, ultra-low dose; ULD50, ultra-low dose CT with 50% ASIR-V reconstruction, ULD 100, ultra-low dose CT with 100% ASIR-V reconstruction.

210x297mm (300 x 300 DPI)

Trial registration data set :

Primary registry and trial identifying number	ClinicalTrials.gov NCT03305978
Date of registration in primary registry	September 26, 2017
Secondary identifying numbers	38RC17.132
Source(s) of monetary or material support	University Hospital, Grenoble
Primary sponsor	University Hospital, Grenoble
Secondary sponsor(s)	French Thoracic Imaging Society
Contact for public queries	Emilie CHIPON, PhD, +33476767313, echipon@chu-grenoble.fr
Contact for scientific queries	Gilbert FERRETTI, MD PhD, +3376767313, gferretti@chu-grenoble.fr
Public title	Pulmonary Nodule Detection: Comparison of an Ultra Low Dose vs Standard Scan.
Scientific title	Detection of Pulmonary Nodules: Comparison of Ultra-low-dose Chest CT (Approaching a Two Views Chest X-ray Radiation) and Standard Low Dose CT. A Monocentric, Prospective, Non-randomized, Comparative, Open-label Study With Blind Reading of the Judgment Criteria
Country of recruitment	France
Health condition(s) or problem(s) studied	Lung cancer screening, radiation exposure
Intervention(s)	Device: Ultra low dose chest CT An additional ultra low dose CT row is performed for every subject besides standard diagnostic low dose chest CT. Other Name: Revolution CT (GE Healthcare) 442507CN0, equiped with ASIR V
	Device: Low dose chest CT standard diagnostic low dose chest CT Other Name: Revolution CT (GE Healthcare)
Key inclusion and exclusion criteria	Ages eligible for study: ≥18 years Sexes eligible for study: both Accepts healthy volunteers: no
	Inclusion criteria : Patients referred for non enhanced chest CT for following indications : - lung nodule search or control - nodular abnormality on chest X ray - statement of COPD or emphysema - asbestos exposure - nodule localization before radio frequency ablation - assessment of disease extent of an extra thoracic cancer (in case of iodinated intravenous contrast agent contraindication) - statement before extrathoracic transplantation (in case of iodinated intravenous contrast agent contraindication) Affiliated with the french social security Who signed consent
	Exclusion criteria : Inability to lie down and stay still during the examination Inability to hold breath more than 5 seconds Pneumonia in the last 3 months Body mass index more than 35kg/m² exclusion period of another interventionnal study

	referred for articles L1121-5 to L1121-8 of french public health code Pregnant or breastfeeding women
Study type	Interventional
	Allocation: Non-Randomized Intervention Model: Sequential Assignment Intervention Model Description: Major Patient Addressed for Thoracic CT without Injection of Contrast Masking: Single (Outcomes Assessor) Masking Description: blinding evaluation of criteria
	Primary purpose: diagnostic
Date of first enrolment	October 3, 2017
Target sample size	150
Recruitment status	Recruiting
Primary outcome(s)	Ultra low dose CT lung nodule detection sensibility [Time Frame: 22 months] Detection rate (%) of ≥4mm lung nodules in ultra low dose chest CT versus standard low
Key secondary outcomes	- Ultra low dose CT diagnostic performances of lung nodule detection [Time Frame: 22 months] :true positives, false positives, true negatives, false negatives, positive predictive value, negative predictive value, specificity, of ≥4mm lung nodules detection within ultra low dose chest CT versus standard low dose chest CT - Concordance of ≥4mm lung nodules characteristics between ultra low dose and standard low dose chest CT [Time Frame: 22 months] : comparison of size, density, type (true nodule or intrapulmonary ganglion) of ≥4mm lung nodule between ultra low dose and standard low dose chest CT - Ultra low dose CT inter-observer reproducibility [Time Frame: 22 months] : inter observer reproducibility for size, density and type of ≥4mm lung nodule detected in ultra low dose CT - Influence of subjects characteristics, nodule location, and nodule size on detection between ultra low dose and standard low dose chest CT [Time Frame: 22 months] : analysis of subjects characteristics (age, gender, body mass index), ≥4mm nodule location, and ≥4 mm nodule size on detection between ultra low dose and standard low dose chest CT - Concordance of emphysema characteristics between ultra low dose and standard low dose chest CT [Time Frame: 22 months] : comparison of emphysema detection, type (centrilobular, paraseptal, panlobular, bullous) and distribution between ultra low dose and standard low dose chest CT - Concordance of coronary calcification detection and quantification between ultra low dose and standard low dose chest CT [Time Frame: 22 months] : Comparison of Weston scores between ultra low dose and standard low dose chest CT - Concordance of bronchial abnormalities evaluation between ultra low dose and standard low dose chest CT [Time Frame: 22 months] : comparison of detection of bronchial thickening or dilatation between ultra low dose and standard low dose chest CT
Ethics Review	approved by the relevant ethical committee (Comité de Protection des Personnes, CPP Sud-Est VI, France, CPP Reference: AU1342), on July 7, 2017

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	17
Protocol version	#3	Date and version identifier	18
Funding	#4	Sources and types of financial, material, and other support	16
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1;16
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	2

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6
Objectives	#7	Specific objectives or hypotheses	7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	11
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n/a
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	n/a

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	n/a
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	16
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	n/a
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Data access	#29	Statement of who will have access to the final trial dataset,	19

		and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Detection of pulmonary nodules: a clinical study protocol to compare ultra-low dose chest CT and standard low-dose CT using ASIR-V.

Journal:	*BMJ Open*
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Complete List of Authors:	Ludwig, Marie; Centre Hospitalier Universitaire Grenoble Alpes, service de radiologie et imagerie médicale, pôle imagerie; Universite Grenoble Alpes Faculte de Medecine Chipon, Emilie; INSERM, CIC 1406; Centre Hospitalier Universitaire Grenoble Alpes, pôle recherche Cohen, Julien; Centre Hospitalier Universitaire Grenoble Alpes, service de radiologie et imagerie médicale, pôle imagerie; Universite Grenoble Alpes Faculte de Medecine Reymond, Emilie; Centre Hospitalier Universitaire Grenoble Alpes, service de radiologie et imagerie médicale, pôle imagerie Medici, Maud; INSERM, CIC 1406; Centre Hospitalier Universitaire Grenoble Alpes, pôle recherche Cole, Anthony; Centre Hospitalier Universitaire Grenoble Alpes, service de radiologie et imagerie médicale, pôle imagerie; Universite Grenoble Alpes Faculte de Medecine Moreau Gaudry, Alexandre; INSERM, CIC 1406; Centre Hospitalier Universitaire Grenoble Alpes, pôle recherche Ferretti, Gilbert; Centre Hospitalier Universitaire Grenoble Alpes, service de radiologie et imagerie médicale, pôle imagerie; Universite Grenoble Alpes Faculte de Medecine
Primary Subject Heading:	Radiology and imaging
Secondary Subject Heading:	Oncology, Respiratory medicine, Smoking and tobacco
Keywords:	low dose computed tomography, ultra low dose computed tomography, pulmonary nodule, lung cancer screening, iterative reconstruction

Detection of pulmonary nodules: a clinical study protocol to compare ultra-low dose chest CT and standard low-dose CT using ASIR-V.

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Delegation to Clinical Research and Innovation (DRCI) of Grenoble-Alpes University Hospital

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KEYWORDS

Low dose computed tomography, Ultra low-dose computed tomography, pulmonary nodule, Lung cancer screening, iterative reconstruction

Word count, excluding title page, abstract, article summary, references, figures, tables, and acknowledgements : 4055

ABSTRACT

Introduction:

Lung cancer screening in individuals at risk has been recommended by various scientific institutions. One of the main concerns for CT screening is repeated radiation exposure, with the risk of inducing malignancies in healthy individuals. Therefore, lowering the radiation dose is one of the main objectives for radiologists. The aim of this study is to demonstrate that an ultra-low dose (ULD) chest CT protocol, using recently introduced hybrid iterative reconstruction (ASiR-V, GE medical Healthcare, Milwaukee, WI, USA), is as performant as a standard "low dose" (LD) CT to detect non calcified lung nodules ≥ 4mm.

Methods and analysis:

The total number of patients to include is 150. Those are referred for non-enhanced chest CT for detection or follow-up of lung nodule and will undergo an additional unenhanced ULD CT acquisition, the dose of which is on average 10 times lower than the conventional LD acquisition. Total dose of the entire exam (LD + ULD) is lower than the French diagnostic reference level for a chest CT (6.65 milliSievert). ULD CT images will be reconstructed with 50% and 100% ASIR-V, and LD CT with 50%. The 3 sets of images will be read in random order by two pair of radiologists, in a blind test, where patient identification and study outcomes are concealed. Detection rate (sensitivity) is the primary outcome. Secondary outcomes will include concordance of nodule characteristics; inter-observer reproducibility; influence of subjects' characteristics, nodule location, and nodule size; and concordance of emphysema, coronary calcifications evaluated by visual scoring and bronchial alterations between LD and ULD CT. In case of discordance, a third radiologist will arbitrate.

Ethics and dissemination:

The study was approved by the relevant ethical committee. Each study participant will sign an informed consent form.

Trial registration number: *Clinicaltrials.gov* NCT03305978

ARTICLE SUMMARY:

STRENGTHS AND LIMITATIONS OF THIS STUDY

- We will evaluate the sensitivity of an ultra-low dose CT, delivering 10 times less radiation than conventional low-dose CT, to detect lung nodules, in a French population of 150 patients referred for lung nodule check-up or follow-up.
- We will use a recently introduced hybrid iterative reconstruction (ASiR-V) and different levels of ASIR-V will be assessed
- Nodules characteristics will be analyzed in particular the diagnosis of intrapulmonary lymph node, which is a benign lesion.
- Patients with morbid obesity (BMI>35) will not be included as image quality of ultra-low dose CT is not acceptable for those morphotypes.
- Readers will be aware of the type of CT acquisition (LD and ULD) and reconstruction, because they are easily recognizable due to the different level of image noise.

INTRODUCTION

Lung cancer is the deadliest cancer in the world (1), mainly due to the fact that it is often diagnosed at advanced stages that are not surgically curable. The current challenge is therefore to detect lung cancer at early asymptomatic stages. Risk factors such as smoking and occupational exposure (mainly asbestos, silica, arsenic, chromium, iron, coal, ionising radiation) are well known and enable to define the target population for such programs.

The National Lung Screening Trial (NLST) was the first study to show that a low dose (LD) (average effective dose of 1.5mSv) computed tomography (CT) lung cancer screening reduced specific death by 20% (95% CI, 6.8 to 26.7; P=0.004) as compared with chest X Ray (CXR) screening (single-view posteroanterior) in actual or former smokers (>30 pack years) patients between 55 and 74 years old (2).

Other lung cancer screening studies are still in progress in Europe, such as the NELSON study in Belgium and the Netherlands, the results of which are expected to be reported soon (3)

However, the drawback of using LD CT at such doses (<1.5 millisievert (mSv)) is that even though irradiating less than standard chest CT, the radiation exposure is still on average 10 times higher than a 2 views CXR, and may be a risk for induced malignancies in itself. (4)

In this context, great efforts are currently being made by CT manufacturers to reduce the dose and maintain diagnostic quality. Technologies such as automated exposure control, lower tube current and iterative reconstruction (5), were recently introduced, enabling further dose decrease for chest CTs, and the concept of “ultra-low dose (ULD) CT” (or submillisievert CT), which delivers a radiation dose approaching that of 2 CXR views at the cost of a slight deterioration of the image quality (6) . Among these technological advances, the most significant is probably the new iterative reconstruction whether full iterative or hybrid. (7,8,9,10)

Promising results have been published for lung nodule detection with ULD CT (11,12,13). However, these studies were conducted on Asian populations, which may have different morphotypes compared to Caucasian populations.

Huber and al. performed a phantom study comparing standard, LD and ULD CT for detection of pulmonary nodules. When compared to standard CT, the detection rate was 95.5% for LD CT (1.76 mSv), and 93.3% for ULD CT (0.13mSv), increasing at 97.5% when adding computer aided diagnosis and maximal intensity projection (14).

Since we started to design our study protocol, Messerli and al. published a study including 202 patients referred for any clinically indicated chest CT. 91.2% nodules were detected using ULD CT (0.13+/-0.01mSv) as compared to LD CT (1.8 ± 0.7 mSv). Sensitivity was significantly higher for larger nodule diameter, lower BMI patients, lower image noise and for solid and calcified nodules (15).

Neroladaki and al. showed the same number of detected nodules between an ULD acquisition (0.16±0.006mSv) with iterative reconstruction and a standard dose filtered back projection acquisition (11.2±2.7mSv), and more nodules detected with model based iterative reconstruction (MBIR) than adaptive statistical iterative reconstruction (ASIR) (16). MBIR is known to better minimize image noise compared to ASIR : Ichikawa and al found a significantly lower image noise with LD (1.6 ± 0.8 mSv) MBIR CT (11.6 ± 1.0 Hounsfield units (HU)) than with LD ASIR CT (21.1 ± 2.6 HU, $p < 0.0005$), a slightly better image quality score for decreased lung attenuation lesion, and no difference in image quality scores for consolidation or mass, ground-glass attenuation, or reticular opacity with MBIR compared to ASIR LD CT (8). But MBIR may slightly deteriorate lesion margin (9), and significantly increases reconstruction time, taking more than 30 minutes, when patients lie less than 10 minutes in the machine. ASIR-V is the latest generation of hybrid iterative reconstruction (GE medical Healthcare, Milwaukee, WI). It combines ASIR and MBIR and enables a better noise reduction than ASIR, with a processing time of only few minutes, suitable to a routine chest CT session (17).

According to the ALARA (as low as reasonably achievable) principle, we hope to validate our ULD chest CT protocol (<0.2mSv), the dose of which is 10 times lower than a usual LD CT, as a

sensitive tool to detect lung nodules. Thus, this ULD CT acquisition could be generalized for lung nodules detection and would consolidate the setup of lung cancer screening programs. Also, this would allow the generalization of ULD protocols, for radiation sensitive populations (children and young adults in particular).

METHODS AND ANALYSIS

Study design and objectives

The objectives of this study are to evaluate the performance of ULD CT for the detection of lung nodules, and the evaluation of nodule characteristics in comparison to LD CT. Furthermore**,** as smoking is a common risk factor, performance for the detection of cardiac and respiratory associated diseases (bronchial abnormalities, emphysema, coronary calcifications) is also evaluated.

An additional ULD CT is performed in patients referred for non-enhanced chest CT for lung nodules check-up or follow-up. The dose delivered with both acquisitions is still lower than the French diagnostic reference level (6.65mSv). We chose to only include nodules ≥ 4mm as the incidence of cancer is very low below this threshold, and are not currently considered as clinically significant (18). A 4 mm threshold was also used for the NLST study (2). In addition, fully calcified nodules are excluded from the analysis because they are constantly benign and easily detected.

We will study nodule subtypes (solid, part-solid and pure ground-glass) and size. Furthermore we will evaluate the performance of ULD CT to diagnose intrapulmonary lymph nodes, which are benign nodules not needing follow up (19), and were not analyzed in previous ULD CT studies.

This trial sponsored by the Grenoble-Alpes University Hospital (CHUGA, France) is designed as a monocentric, prospective, non-randomized study in which the patient is his own control. All outcomes are evaluated by blinded double reading. Patient enrollment started in October 2017 and is expected to be completed in September 2018. Figure 1 summarizes the process of inclusion, intervention and reading, described in detail below.

Primary outcome

Detection rate (sensitivity) of lung nodules in ULD chest CT using the conventional chest LD CT as gold-standard.

Secondary outcomes

1) Diagnostic criteria: true positive (TP), false positive (FP), true negative (TN), false negative (FN), positive predictive value (PPV), negative predictive value (NPV), Specificity (Sp) of ULD CT

2) Concordance of nodule's size, subtype, and diagnosis of typical intrapulmonary lymph node among lung nodules between ULD and LD CT

3) Inter-observer reproducibility for size, subtype and diagnosis of lung nodules in ULD CT

4) Influence of subjects characteristics (age, sex, BMI), nodule location, and nodule size on lung nodule detection with ULD CT

5) Concordance of emphysema detection, type and distribution between ULD and LD CT

6) Concordance of Weston score of coronary calcifications between ULD and LD CT

7) Concordance of visual assessment of bronchial thickening, mucoid impaction or dilatation between ULD and LD CT

Eligibility Criteria

Inclusion criteria

- aged 18 years or older
- referred for non-enhanced chest CT for the following indications:
  - lung nodule check-up or follow-up
  - nodular abnormality on chest X ray
  - morphologic assessment of chronic obstructive pulmonary disease (COPD) or emphysema
  - asbestos exposure
  - assessment before lung radio frequency ablation

- assessment of disease extent of an extra thoracic cancer (in case of iodinated intravenous contrast agent contraindication)
- Check-up before extra-thoracic transplantation (in case of iodinated intravenous contrast agent contraindication).

Exclusion criteria

- Inability to lie down and stay still during the examination
- Inability to hold breath for more than 5 seconds
- Pneumonia in the last 3 months
- Body mass index (BMI) more than 35kg/m²
- Pregnant or breastfeeding women

CT scan acquisitions and reconstructions

The LD and ULD acquisitions are performed on the Revolution CT scanner (GE medical Healthcare, Milwaukee, WI, USA) equipped with the third generation ASIR-V iterative reconstruction. Acquisitions are performed successively in the same CT exam, in the supine position and at suspended full inspiration. Both acquisitions cover the same pulmonary fields from the apex to the costo-diaphragmatic angle, determined on the scout views (2 views).

The LD acquisition is the reference exam for the diagnosis of pulmonary nodules. The acquisition parameters are: spiral CT scanning; 120kVp; automatic modulation of 3D radiation dose ("Smart mA"+ Organ Dose Modulation) with lower bound 100mA, maximal bound 200mA and noise index 10; rotation time: 0.35sec ; modulation 35-70 mAs; pitch = 0.992 :1 and collimation: 80mm. The radiation dose, CTDIvol (volume CT dose index) and DLP (Dose Length Product = CTDIvol x length of exposure) may vary depending on patient attenuation and length of the acquisition. The expected DLP is between 70 and 200mGy.cm (0.98mSv to 2.8mSv) (the effective dose is calculated

by multiplying DLP by a thoracic conversion factor of 0.014 (20)), for an average DLP of 100mGy.cm.

The ULD CT acquisition parameters are: spiral CT scanning; 120kVp; fixed tube current of 10mA; rotation time: 0.35s; 3.5 mAs; pitch: 0.992 :1, collimation: 80mm. These parameters are fixed for all patients. The CTDIvol is constant at 0.24mGy. The DLP will depend only on the length of the acquired chest, different for each patient, expected around 10mGy.cm (0.14mSv). The modulation of the mA is deactivated to allow a very low tube current and therefore an ULD acquisition. The ULD acquisition increases the exam time by up to two minutes.

The reconstruction parameters are identical for both acquisitions: slice thickness: 1.25mm; standard filter and lung filter; contiguous 8-mm thickness Maximal Intensity projection (MIP) reconstruction, and iterative reconstruction with different percentages. We use ASIR-V in our study which is the latest generation of iterative reconstruction techniques. It blends hybrid iterative reconstruction and standard filtered back projection. The percentage of ASIR-V represents the amount of iterative reconstruction, from 0% (filtered back projection only) to 100% iterative reconstruction, which modifies image noise and texture. When designing our study, ASIR-V was not yet studied for chest CT. The CT vendor engineers suggested an empirical percentage between 40 up to 100%, depending on radiologist practice and preferences. We decided to test percentages of iterative reconstruction of 50% and 100%. The LD CT images are reconstructed with 50% ASIR-V (LD) and the ULD CT images with 50% (ULD50) and 100% (ULD100) ASIR-V.

The statistical analyses will be performed twice: with ULD50 and ULD100.

For every patient, CTDIvol and DLP are recorded. Effective dose and Size Specific Dose Estimates (SSDE) will be then calculated. Concerning the additional radiation for included patients, our ULD CT protocol has an expected effective dose between 0.10 and 0.20 mSv, which is about 6 to 20 times lower than the LD protocol (which is the usual dose in our institution for this indication), similar to a 2-views CXR, and to 30 days of natural radiation (21). Moreover, total dose of the entire exam (around 1.1 to 3 mSv) is lower than French diagnostic reference level of 6.65mSv.

Recruitment and intervention

Patients included in the study are those referred for a diagnostic chest CT without contrast media injection. On the day of the CT scan, a radiologist checks the eligibility criteria for the study, and informs the patient who signs a participation consent form if he accepts to join the study. The radiologist then collects the following parameters: height, weight, history of oncology, cardio-respiratory pathology and exposure to smoking. The patient then undergoes the standard diagnostic LD CT acquisition followed by the ULD acquisition. If, however, the dose of the LD acquisition is greater than 6.65mSv (French diagnostic reference level), the ULD acquisition is not performed and the patient is excluded from the data analysis. The patient's participation in the study is completed once he leaves the examination room.

The CT images of the LD acquisition are analysed by the radiologist who gives his medical report for the patient's medical management. If the number of nodules ≥ 4 mm identified on this acquisition is ≥6 in one lung, the patient will be excluded from the data analysis because the analysis of the outcomes will be too complicated to implement.

Patient and Public Involvement

Patients or public were not directly involved in the development of the research question. However, lowering the radiation dose is a rising concern for the patients and for public health. Patients were also not directly involved in the design, the recruitment and the conduct of this study.

As a regular medical care, the report of the diagnostic LD CT is sent to the prescribing physician, and to the patients at their request. According to French law, patients will be informed of the global results of the study at their request.

Blind reading of outcomes

For LD, ULD50 and ULD100 reconstructions, 2 radiologists will independently read all the radiological parameters. In order to limit the number of exams assessed by each reader, 4

radiologists split into 2 pairs will participate in the blind reading. Each pair of radiologists (1 junior and 1 senior radiologist) reads the three sets of images for the same patient in a random order.

The term “blind” means that radiologists have neither knowledge of the patient's identity nor access to the results of diagnostic reading. To avoid patient identification, CT acquisitions are anonymized by deleting in the DICOM fields: the name, age and date of birth of the patient; the date and time of the examination and the name of the referring radiologist for the diagnosis. Each patient reconstruction is identified by a random number that differs for each of the two readers. Radiologists never read two series of the same patient consecutively.

Anonymized exams are periodically transmitted to a pair with at least 15 LD, 15 ULD50 and 15 ULD100 reconstructions. The three patient reconstructions are not necessarily given the same day to both radiologists. In addition, the order of presentation is not identical for the two radiologists.

The reading is performed on a diagnostic console (IMPAX software, 6.5.5.3502) (Agfa, Belgium) using Barco MDNC-3121monitors (Barco, Courtrai, Belgium) and includes mediastinal and parenchymal filter reconstructions for each acquisition. The radiologist is free to adapt the level and width of the window to its reading practice (initial parenchymal window defined by a width of 1500UH and a level of -600UH), and to perform multiplanar reconstructions in the different plans of space. The reading also includes the additional MIP reconstruction for each acquisition, in order to sensitize the detection of nodules (22) (this type of reading from MIP series is performed in clinical routine).

Radiologists identify nodules of longer diameter ≥4mm by locating them with the slice number and the lobe. It is known that each lung has three lobes (right upper lobe, middle lobe, right lower lobe, culmen, lingula, and left lower lobe). Each radiologist completes a reading grid for each reconstruction with all detected nodule characteristics, evaluation of emphysema, coronary calcification and bronchial abnormalities.

The completed grids are given to a Clinical Research Assistant for data entry and identification of discrepancies in identification of nodules between the two radiologists.

We consider that a nodule is the same between the two readers if:

- it is located in the same lobe
- the slice number is identical at ± 5 slices (a nodule will be visible on several successive slices)
- the longest diameter of nodule is the same at ± 2mm (23)

If these criteria are not respected or if a radiologist identifies one or more nodules in addition to or less than the second radiologist, a consensus with a third CHUGA senior thoracic radiologist with 27 years of experience is obtained. This third radiologist is not part of the reading pairs. The consensus is made from anonymized reconstructions and the reconstructions of the same patient are not processed successively.

Besides, for every reconstruction is recorded:

- noise by measuring standard deviation in a region of interest placed in the tracheal air above the carina,
- shape of the trachea which indicates inspiration degree,
- subjective image quality on a 3-point scale.

Data monitoring

All data is monitored by Grenoble-Alpes University Hospital (trial sponsor), in order to verify that for every patient enrolled there is a signed consent form and that the inclusion and exclusion criteria are respected. In addition all data collected in the case report form of every enrolled patient are verified.

Sample size

With a 90% power, to have a sensitivity of detection of nodules with the ULD CT to 90% with a confidence interval to ±10%, it would be necessary to analyze 124 nodules. According to a retrospective analysis of patients with indication of pulmonary nodule CT made at CHUGA, out of

420 patients per year with this indication, 210 present pulmonary nodules with a total of about 400 nodules. It should therefore include about 140 patients to have 124 nodules to be analyzed. Considering a 5% potential loss to follow-up or withdrawal of consent, the actual number of subjects to include is 147 in total. To this are added three potential patients who could be secondarily excluded from the study for a number of nodules ≥6 in one of the lungs. The total number of patients to include is 150. The sample size calculations were carried out using R software version 3.1.0 (library MKmisc, function power.diagnostic.test) (24, 25, 26).

Statistical analysis

In this non-randomized study where each patient is his own control, the threshold $p<0.05$ will be taken into account to define the significance of the statistical tests. Analyses will be carried out in accordance with good statistical analysis practices after freezing of the database and will be carried out with the software R (version ≥ 3.1.0). If the missing data rate of the primary criterion is between 5% and 20%, the missing data for this criterion will be replaced. The replacement of the missing data will be done, either according to a worst-case analysis strategy, by disfavoring the assumption that one seeks to demonstrate, either by a multiple imputation method. In case of multiple imputations, five imputations will be made, using a linear regression model taking into account the following variables: age, sex, BMI, smoking habit.

The normality of the quantitative parameters will be determined by the Shapiro-Wilks test or by graphical verification of the symmetry of the distribution. When the normality of the distribution of such a parameter has been demonstrated, it will be described by its mean and its standard deviation. Otherwise it will be described by its median, the 25th and the 75th percentile. The qualitative parameters will be expressed in number and percentage.

For the main objective, the sensitivity of the ULD CT (compared to the LD CT) for the detection of nodules will be calculated and accompanied by a 95% confidence interval. For secondary objective 1, the number of TP, FP, TN, FN, PPV, NPV and Sp of the ULD CT (compared to LD CT) will be

calculated. For secondary objectives 2, 5, 6 and 7, the concordance of the qualitative variables will be evaluated using the kappa coefficient. The concordance of the quantitative variables will be evaluated using Lin's concordance coefficient. For each coefficient, the 95% confidence interval will be given. For secondary objective 3, inter-observer reproducibility for qualitative variables will be evaluated using the kappa coefficient. It will be evaluated, for the quantitative variables, using the ICC (intra class coefficient). For each coefficient, the 95% confidence interval will be given. For secondary objective 4, a logistic regression model will be implemented. The variable to be explained will be the result of detecting each nodule in ULD CT compared to the LD CT (0 = good detection / 1 = bad detection). The explanatory variables will be the age, sex and BMI of the patient, the location (lobe) and the size of the nodule. The size of the nodule can be used as a qualitative variable (<5mm, 5-10mm,> 10mm).

An interim analysis including the analysis of the primary endpoint will be performed after inclusion of the first 50 patients. This interim analysis will aim to: decide whether to continue or stop the study for futility and readjust the number of patients if necessary (if the characteristics of the patients included do not correspond to those initially planned (too many patients without nodules ≥4 mm)). In order to maintain an overall threshold of 5% in the final analysis, the interim analysis will be carried out with a threshold of 0.1%. The results of the interim analysis will be taken into account by the steering committee to propose modifications to the analysis plan. For this interim analysis, data from the confrontation between the two radiologists will be used.

Limitations

First limitation of our protocol is that we do not have a true screening population because there is no organized lung cancer screening program in our country yet. Therefore, our study population corresponds to patients routinely referred for lung nodule checkup or follow up instead of a risk-factor based population.

Another limitation is that ULD CT is easily recognizable as the image noise is increased as compared to LD CT, as well as ULD 50 and ULD 100 are possible to distinguish for an experienced radiologist. As a consequence, readers were not blinded for these, but for patient name, sex, age, clinical status, and CT report.

Recall bias is limited by a randomized order of presentation and cutting into several reading sessions.

Although we wanted to have a "western population", we decided not to include obese patients with a BMI>35, because ULD CT are of poorer quality, due to the need of more radiation-exposure to produce acceptable images. Vardhanabhuti and al. recently found a loss of nodule detection with iterative reconstructed CT scanners at an effective dose of 0.14±0.01mSv for obese patients with BMI>38 (27).

We decided to test percentage of 50 and 100% of ASIR-V. Tang and al. tested ASIR-V from 10 to 100% in non-enhanced chest and showed ASIR-V has greater potential in reducing image noise and artifacts and maintaining image sharpness when compared to ASIR, and 60% ASIR-V had the highest image quality combining both the objective and subjective evaluation of images (28). This finding, although occurring after the design of our study is close to our chosen 50% level of ASIR-V.

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AUTHOR CONTRIBUTIONS

M. Ludwig is the corresponding author and contributed to the conception of the study, to the inclusion of patients, to the blind reading of outcomes and to the drafting of the manuscript.

E. Chipon contributed to the conception of the study, to the drafting of the manuscript, and is responsible for data management and its integrity.

J. Cohen contributed to the conception of the study, to the inclusion of patients, to the blind reading of outcomes and to the revision of the manuscript.

E. Reymond contributed to the inclusion of patients, to the blind reading of outcomes and to the revision of the manuscript.

M. Medici contributed to the design and application of statistical analysis, and to the drafting of the manuscript.

A. Cole contributed to the blind reading of outcomes and to the revision of the manuscript.

A. Moreau Gaudry contributed to the conception of the study and to the revision of the manuscript.

G R Ferretti is the principal investigator of the study and contributed to the conception of the work, to the inclusion of patients, to the blind consensus of outcomes and to the revision of the manuscript.

All authors approved the final manuscript and agreed to be accountable for all aspects of the work.

COMPETING INTERESTS

The authors declare that they have no competing interests

CONSENT FOR PUBLICATION

Not applicable

ETHICS AND DISSEMINATION

This trial is registered on the ClinicalTrials.gov database (reference NCT03305978) (see supplementary file “trial registration data set”), and was approved by the relevant ethical committee (Comité de Protection des Personnes, CPP sud-est VI, France, 07/07/2017, CPP Reference: AU1342). The Protocol version is N°1.0- Date: May 4th 2017

All patients sign a consent form before being enrolled in the trial, in accordance with the Declaration of Helsinki II.

Once the statistical report is finalized, we plan to publish our results in an international scientific journal and present them in national and international congresses.

DATA STATEMENT

Legal restrictions (French personal data laws) prohibit the authors from making the minimal data set publicly available. These data are available upon request.

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REFERENCES

1. Globocan : Lung Cancer Estimated Incidence, Mortality and Prevalence Worldwide in 2012 http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx)
2. National Lung Screening Trial Research Team, Denise R. Aberle, Amanda M. Adams, Christine D. Berg, William C. Black, Jonathan D. Clapp, Richard M. Fagerstrom, et al. "Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening." *The New England Journal of Medicine* 365, no. 5 (August 4, 2011): 395–409. doi:10.1056/NEJMoa1102873
3. Yousaf-Khan U, van der Aalst C, de Jong PA, et al."Final screening round of the NELSON lung cancer screening trial: the effect of a 2.5-year screening interval." Thorax 2017;72:48-56. 10.1136/thoraxjnl-2016-208655

4. Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation and National Research Council. Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2.Washington, D.C: The National Academies Press; 2006
5. Kubo T, Ohno Y, Seo JB, Yamashiro T, Kalender WA, Lee CH, et al. "Securing safe and informative thoracic CT examinations-Progress of radiation dose reduction techniques". Eur J Radiol. 2017 Jan;86:313–9.
6. Kim, Yookyung, Yoon Kyung Kim, Bo Eun Lee, SeokJeong Lee, YonJuRyu, Jin Hwa Lee, and Jung Hyun Chang. "Ultra-Low-Dose CT of the Thorax Using Iterative Reconstruction: Evaluation of Image Quality and Radiation Dose Reduction." *AJR. American Journal of Roentgenology* 204, no. 6 (June 2015): 1197–1202. doi:10.2214/AJR.14.13629.
7. Vardhanabhuti, Varut, Robert J. Loader, Grant R. Mitchell, Richard D. Riordan, and Carl A. Roobottom. "Image Quality Assessment of Standard- and Low-Dose Chest CT Using Filtered Back Projection, Adaptive Statistical Iterative Reconstruction, and Novel Model-Based Iterative Reconstruction Algorithms." *AJR. American Journal of Roentgenology* 200, no. 3 (March 2013): 545–52. doi:10.2214/AJR.12.9424.
8. Ichikawa, Yasutaka, Kakuya Kitagawa, Naoki Nagasawa, Shuichi Murashima, and Hajime Sakuma. "CT of the Chest with Model-Based, Fully Iterative Reconstruction: Comparison with Adaptive Statistical Iterative Reconstruction." *BMC Medical Imaging* 13 (2013): 27. doi:10.1186/1471-2342-13-27.
9. Padole, Atul, Sarabjeet Singh, Jeanne B. Ackman, Carol Wu, Synho Do, Sarvenaz Pourjabbar, Ranish Deedar Ali Khawaja, et al. "Submillisievert Chest CT with Filtered Back Projection and Iterative Reconstruction Techniques." *AJR. American Journal of Roentgenology* 203, no. 4 (October 2014): 772–81. doi:10.2214/AJR.13.12312.
10. Montet, Xavier, Anne-Lise Hachulla, Angeliki Neroladaki, Frederic Lador, Thierry Rochat, Diomidis Botsikas, and Christoph D. Becker. "Image Quality of Low mA CT Pulmonary Angiography Reconstructed with Model Based Iterative Reconstruction versus Standard CT

Pulmonary Angiography Reconstructed with Filtered Back Projection: An Equivalency Trial." *EuropeanRadiology* 25, no. 6 (June 2015): 1665–71. doi:10.1007/s00330-014-3563-5.

11. Yoon, Hyun Jung, Myung Jin Chung, Hye Sun Hwang, Jung Won Moon, and Kyung Soo Lee. "Adaptive Statistical Iterative Reconstruction-Applied Ultra-Low-Dose CT with Radiography-Comparable Radiation Dose: Usefulness for Lung Nodule Detection." *Korean Journal of Radiology* 16, no. 5 (October 2015): 1132–41. doi:10.3348/kjr.2015.16.5.1132
12. Sui, Xin, Felix G. Meinel, Wei Song, Xiaoli Xu, Zixing Wang, Yuyan Wang, Zhengyu Jin, Jiuhong Chen, Rozemarijn Vliegenthart, and U. Joseph Schoepf. "Detection and Size Measurements of Pulmonary Nodules in Ultra-Low-Dose CT with Iterative Reconstruction Compared to Low Dose CT." *European Journal of Radiology* 85, no. 3 (March 2016): 564–70. doi:10.1016/j.ejrad.2015.12.013
13. Nagatani Y, Takahashi M, Murata K, Ikeda M, Yamashiro T, Miyara T, Koyama H, Koyama M, Sato Y, Moriya H, et al "Lung nodule detection performance in five observers on computed tomography (CT) with adaptive iterative dose reduction using three-dimensional processing (AIDR 3D) in a Japanese multicenter study: Comparison between ultra-low-dose CT and low-dose CT by receiver-operating characteristic analysis".*Eur J Radiol. 2015 Jul; 84(7):1401-12. Epub 2015 Apr 2*
14. Huber, Adrian, Julia Landau, Lukas Ebner, Yanik Bütikofer, Lars Leidolt, Barbara Brela, Michelle May, Johannes Heverhagen, and Andreas Christe. "Performance of Ultralow-Dose CT with Iterative Reconstruction in Lung Cancer Screening: Limiting Radiation Exposure to the Equivalent of Conventional Chest X-Ray Imaging." *EuropeanRadiology*, January 26, 2016. doi:10.1007/s00330-015-4192-3
15. Messerli M, Kluckert T, Knitel M, Wälti S, Desbiolles L, Rengier F, et al. "Ultralow dose CT for pulmonary nodule detection with chest x-ray equivalent dose - a prospective intra-individual comparative study". EurRadiol. 2017 Aug;27(8):3290–9.

16. Neroladaki, Angeliki, Diomidis Botsikas, Sana Boudabbous, Christoph D. Becker, and Xavier Montet. "Computed Tomography of the Chest with Model-Based Iterative Reconstruction Using a Radiation Exposure Similar to Chest X-Ray Examination: Preliminary Observations." *EuropeanRadiology* 23, no. 2 (February 2013): 360–66. doi:10.1007/s00330-012-2627-7.

17. De Marco P, Origgi D. "New adaptive statistical iterative reconstruction ASiR-V: Assessment of noise performance in comparison to ASiR". J Appl Clin Med Phys. 2018 Mar;19(2):275-286. doi: 10.1002/acm2.12253. Epub 2018 Jan 24. PubMed PMID: 29363260; PubMed Central PMCID: PMC5849834

18. Gierada DS, Pinsky P, Nath H, Chiles C, Duan F, Aberle DR. "Projected outcomes using different nodule sizes to define a positive CT lung cancer screening examination". J Natl Cancer Inst. 2014;106:dju284.

19. Ahn MI, Gleeson TG, Chan IH et-al. "Perifissural nodules seen at CT screening for lung cancer". Radiology. 2010;254 (3): 949-56. doi:10.1148/radiol.09090031

20. Task Group on Control of Radiation Dose in Computed Tomography. "Managing Patient Dose in Computed Tomography. A Report of the International Commission on Radiological Protection." *Annals of the ICRP* 30, no. 4 (2000): 7–45

21. Exposition de la population française aux rayonnements ionisants liée aux actes de diagnostic médical en 2012. Rapport IRSN PRP-HOM N°2014-6

22. Jankowski, A., T. Martinelli, J. F. Timsit, C. Brambilla, F. Thony, M. Coulomb, and G. Ferretti. "Pulmonary Nodule Detection on MDCT Images: Evaluation of Diagnostic Performance Using Thin Axial Images, Maximum Intensity Projections, and Computer-Assisted Detection." European Radiology 17, no. 12 (December 2007): 3148–56. doi:10.1007/s00330-007-0727-6.

23. Revel MP, Bissery A, Bienvenu M, Aycard L, Lefort C, Frija G. Are two-dimensional CT measurements of small noncalcified pulmonary nodules reliable? Radiology. 2004 May;231(2):453-8. PubMed PMID: 15128990.

24. A. Flahault, M. Cadilhac, and G. Thomas (2005). Sample size calculation should be performed for design accuracy in diagnostic test studies. Journal of ClinicalEpidemiology, 58(8):859-862.

25. H. Chu and S.R. Cole (2007). Sample size calculation using exact methods in diagnostic test studies. Journal of ClinicalEpidemiology, 60(11):1201-1202.

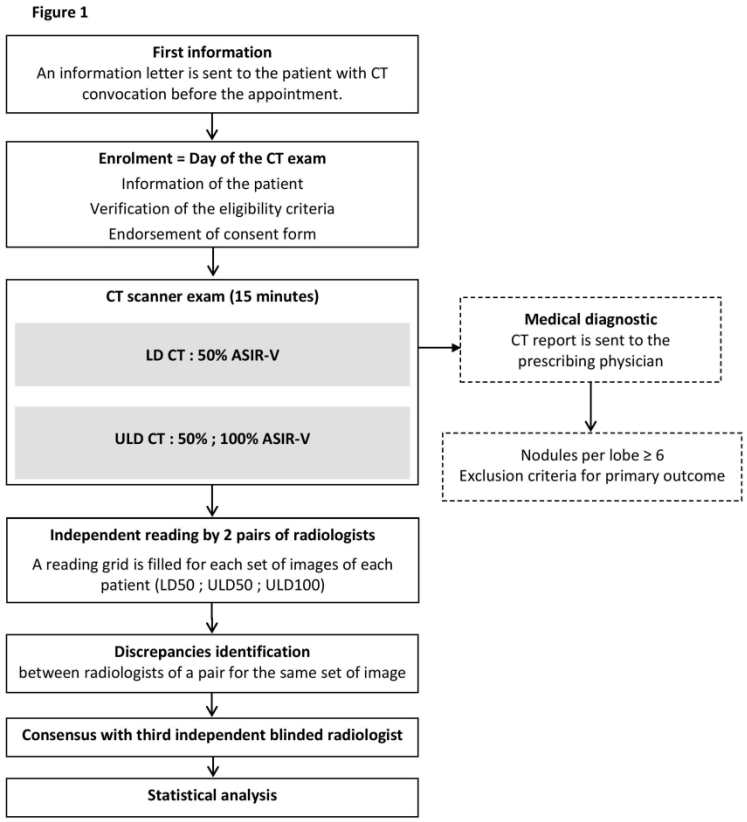
26. M.R. Chernickamd C.Y. Liu (2002). The saw-toothed behavior of power versus sample size and software solutions: single binomial proportion using exact methods. Am Stat, 56:149-155.

27. Vardhanabhuti V, Pang CL, Tenant S, Taylor J, Hyde C, Roobottom C. "Prospective intra-individual comparison of standard dose versus reduced-dose thoracic CT using hybrid and pure iterative reconstruction in a follow-up cohort of pulmonary nodules-Effect of detectability of pulmonary nodules with lowering dose based on nodule size, type and body mass index". Eur J Radiol. 2017 Jun;91:130-141. doi: 10.1016/j.ejrad.2017.04.006

28. Tang H, Yu N, Jia Y, Yu Y, Duan H, Han D, et al. "Assessment of noise reduction potential and image quality improvement of a new generation adaptive statistical iterative reconstruction (ASIR-V) in chest CT". Br J Radiol. 2018 Jan;91(1081):20170521

FIGURE 1 legend:

Study Flow chart. ASIR-V ®, adaptive statistical iterative reconstruction-Véo (GE medical Healthcare, Milwaukee, WI, USA); CT, computed tomography; LD, low dose; LD50, low dose CT with 50% ASIR-V reconstruction; ULD, ultra-low dose; ULD50, ultra-low dose CT with 50% ASIR-V reconstruction, ULD 100, ultra-low dose CT with 100% ASIR-V reconstruction



Study Flow chart. ASIR-V ®, adaptive statistical iterative reconstruction-Véo (GE medical Healthcare, Milwaukee, WI, USA); CT, computed tomography; LD, low dose; LD50, low dose CT with 50% ASIR-V reconstruction; ULD, ultra-low dose; ULD50, ultra-low dose CT with 50% ASIR-V reconstruction, ULD 100, ultra-low dose CT with 100% ASIR-V reconstruction.

210x297mm (300 x 300 DPI)

Trial registration data set :

Primary registry and trial identifying number	ClinicalTrials.gov NCT03305978
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Primary sponsor	University Hospital, Grenoble
Secondary sponsor(s)	French Thoracic Imaging Society
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Contact for scientific queries	Gilbert FERRETTI, MD PhD, +3376767313, gferretti@chu-grenoble.fr
Public title	Pulmonary Nodule Detection: Comparison of an Ultra Low Dose vs Standard Scan.
Scientific title	Detection of Pulmonary Nodules: Comparison of Ultra-low-dose Chest CT (Approaching a Two Views Chest X-ray Radiation) and Standard Low Dose CT. A Monocentric, Prospective, Non-randomized, Comparative, Open-label Study With Blind Reading of the Judgment Criteria
Country of recruitment	France
Health condition(s) or problem(s) studied	Lung cancer screening, radiation exposure
Intervention(s)	Device: Ultra low dose chest CT An additional ultra low dose CT row is performed for every subject besides standard diagnostic low dose chest CT. Other Name: Revolution CT (GE Healthcare) 442507CN0, equiped with ASIR V
	Device: Low dose chest CT standard diagnostic low dose chest CT Other Name: Revolution CT (GE Healthcare)
Key inclusion and exclusion criteria	Ages eligible for study: ≥18 years Sexes eligible for study: both Accepts healthy volunteers: no
	Inclusion criteria : Patients referred for non enhanced chest CT for following indications : - lung nodule search or control - nodular abnormality on chest X ray - statement of COPD or emphysema - asbestos exposure - nodule localization before radio frequency ablation - assessment of disease extent of an extra thoracic cancer (in case of iodinated intravenous contrast agent contraindication) - statement before extrathoracic transplantation (in case of iodinated intravenous contrast agent contraindication) Affiliated with the french social security Who signed consent
	Exclusion criteria : Inability to lie down and stay still during the examination Inability to hold breath more than 5 seconds Pneumonia in the last 3 months Body mass index more than 35kg/m² exclusion period of another interventionnal study

	referred for articles L1121-5 to L1121-8 of french public health code Pregnant or breastfeeding women
Study type	Interventional
	Allocation: Non-Randomized Intervention Model: Sequential Assignment Intervention Model Description: Major Patient Addressed for Thoracic CT without Injection of Contrast Masking: Single (Outcomes Assessor) Masking Description: blinding evaluation of criteria
	Primary purpose: diagnostic
Date of first enrolment	October 3, 2017
Target sample size	150
Recruitment status	Recruiting
Primary outcome(s)	Ultra low dose CT lung nodule detection sensibility [Time Frame: 22 months] Detection rate (%) of ≥4mm lung nodules in ultra low dose chest CT versus standard low
Key secondary outcomes	- Ultra low dose CT diagnostic performances of lung nodule detection [Time Frame: 22 months] :true positives, false positives, true negatives, false negatives, positive predictive value, negative predictive value, specificity, of ≥4mm lung nodules detection within ultra low dose chest CT versus standard low dose chest CT - Concordance of ≥4mm lung nodules characteristics between ultra low dose and standard low dose chest CT [Time Frame: 22 months] : comparison of size, density, type (true nodule or intrapulmonary ganglion) of ≥4mm lung nodule between ultra low dose and standard low dose chest CT - Ultra low dose CT inter-observer reproducibility [Time Frame: 22 months] : inter observer reproducibility for size, density and type of ≥4mm lung nodule detected in ultra low dose CT - Influence of subjects characteristics, nodule location, and nodule size on detection between ultra low dose and standard low dose chest CT [Time Frame: 22 months] : analysis of subjects characteristics (age, gender, body mass index), ≥4mm nodule location, and ≥4 mm nodule size on detection between ultra low dose and standard low dose chest CT - Concordance of emphysema characteristics between ultra low dose and standard low dose chest CT [Time Frame: 22 months] : comparison of emphysema detection, type (centrilobular, paraseptal, panlobular, bullous) and distribution between ultra low dose and standard low dose chest CT - Concordance of coronary calcification detection and quantification between ultra low dose and standard low dose chest CT [Time Frame: 22 months] : Comparison of Weston scores between ultra low dose and standard low dose chest CT - Concordance of bronchial abnormalities evaluation between ultra low dose and standard low dose chest CT [Time Frame: 22 months] : comparison of detection of bronchial thickening or dilatation between ultra low dose and standard low dose chest CT
Ethics Review	approved by the relevant ethical committee (Comité de Protection des Personnes, CPP Sud-Est VI, France, CPP Reference: AU1342), on July 7, 2017

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	17
Protocol version	#3	Date and version identifier	18
Funding	#4	Sources and types of financial, material, and other support	16
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1;16
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	2

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6
Objectives	#7	Specific objectives or hypotheses	7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	11
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n/a
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	n/a

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	n/a
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	16
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	n/a
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Data access	#29	Statement of who will have access to the final trial dataset,	19

		and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Detection of pulmonary nodules: a clinical study protocol to compare ultra-low dose chest CT and standard low-dose CT using ASIR-V.

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Primary Subject Heading:	Radiology and imaging
Secondary Subject Heading:	Oncology, Respiratory medicine, Smoking and tobacco
Keywords:	low dose computed tomography, ultra low dose computed tomography, pulmonary nodule, lung cancer screening, iterative reconstruction

Detection of pulmonary nodules: a clinical study protocol to compare ultra-low dose chest CT and standard low-dose CT using ASIR-V.

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KEYWORDS

Low dose computed tomography, Ultra low-dose computed tomography, pulmonary nodule, Lung cancer screening, iterative reconstruction

Word count, excluding title page, abstract, article summary, references, figures, tables, and acknowledgements : 4047

ABSTRACT

Introduction:

Lung cancer screening in individuals at risk has been recommended by various scientific institutions. One of the main concerns for CT screening is repeated radiation exposure, with the risk of inducing malignancies in healthy individuals. Therefore, lowering the radiation dose is one of the main objectives for radiologists. The aim of this study is to demonstrate that an ultra-low dose (ULD) chest CT protocol, using recently introduced hybrid iterative reconstruction (ASiR-V, GE medical Healthcare, Milwaukee, WI, USA), is as performant as a standard "low dose" (LD) CT to detect non calcified lung nodules ≥ 4mm.

Methods and analysis:

The total number of patients to include is 150. Those are referred for non-enhanced chest CT for detection or follow-up of lung nodule and will undergo an additional unenhanced ULD CT acquisition, the dose of which is on average 10 times lower than the conventional LD acquisition. Total dose of the entire exam (LD + ULD) is lower than the French diagnostic reference level for a chest CT (6.65 milliSievert). ULD CT images will be reconstructed with 50% and 100% ASIR-V, and LD CT with 50%. The 3 sets of images will be read in random order by two pair of radiologists, in a blind test, where patient identification and study outcomes are concealed. Detection rate (sensitivity) is the primary outcome. Secondary outcomes will include concordance of nodule characteristics; inter-observer reproducibility; influence of subjects' characteristics, nodule location, and nodule size; and concordance of emphysema, coronary calcifications evaluated by visual scoring and bronchial alterations between LD and ULD CT. In case of discordance, a third radiologist will arbitrate.

Ethics and dissemination:

The study was approved by the relevant ethical committee. Each study participant will sign an informed consent form.

Trial registration number: *Clinicaltrials.gov* NCT03305978

ARTICLE SUMMARY:

STRENGTHS AND LIMITATIONS OF THIS STUDY

- We will evaluate the sensitivity of an ultra-low dose CT, delivering 10 times less radiation than conventional low-dose CT, to detect lung nodules, in a French population of 150 patients referred for lung nodule check-up or follow-up.
- We will use a recently introduced hybrid iterative reconstruction (ASiR-V) and different levels of ASIR-V will be assessed
- Nodules characteristics will be analyzed in particular the diagnosis of intrapulmonary lymph node, which is a benign lesion.
- Patients with morbid obesity (BMI>35) will not be included as image quality of ultra-low dose CT is not acceptable for those morphotypes.
- Readers will be aware of the type of CT acquisition (LD and ULD) and reconstruction, because they are easily recognizable due to the different level of image noise.

INTRODUCTION

Lung cancer is the deadliest cancer in the world (1), mainly due to the fact that it is often diagnosed at advanced stages that are not surgically curable. The current challenge is therefore to detect lung cancer at early asymptomatic stages. Risk factors such as smoking and occupational exposure (mainly asbestos, silica, arsenic, chromium, iron, coal, ionising radiation) are well known and enable to define the target population for such programs.

The National Lung Screening Trial (NLST) was the first study to show that a low dose (LD) (average effective dose of 1.5mSv) computed tomography (CT) lung cancer screening reduced specific death by 20% (95% CI, 6.8 to 26.7; P=0.004) as compared with chest X Ray (CXR) screening (single-view posteroanterior) in actual or former smokers (>30 pack years) patients between 55 and 74 years old (2).

Other lung cancer screening studies are still in progress in Europe, such as the NELSON study in Belgium and the Netherlands, the results of which are expected to be reported soon (3)

However, the drawback of using LD CT at such doses (<1.5 millisievert (mSv)) is that even though irradiating less than standard chest CT, the radiation exposure is still on average 10 times higher than a 2 views CXR, and may be a risk for induced malignancies in itself. (4)

In this context, great efforts are currently being made by CT manufacturers to reduce the dose and maintain diagnostic quality. Technologies such as automated exposure control, lower tube current and iterative reconstruction (5), were recently introduced, enabling further dose decrease for chest CTs, and the concept of “ultra-low dose (ULD) CT” (or submillisievert CT), which delivers a radiation dose approaching that of 2 CXR views at the cost of a slight deterioration of the image quality (6). Among these technological advances, the most significant is probably the new iterative reconstruction whether full iterative or hybrid. (7,8,9,10)

Promising results have been published for lung nodule detection with ULD CT (11,12,13). However, these studies were conducted on Asian populations, which may have different morphotypes compared to Caucasian populations.

Huber and al. performed a phantom study comparing standard, LD and ULD CT for detection of pulmonary nodules. When compared to standard CT, the detection rate was 95.5% for LD CT (1.76 mSv), and 93.3% for ULD CT (0.13mSv), increasing at 97.5% when adding computer aided diagnosis and maximal intensity projection (14).

Since we started to design our study protocol, Messerli and al. published a study including 202 patients referred for any clinically indicated chest CT. 91.2% nodules were detected using ULD CT (0.13+/-0.01mSv) as compared to LD CT (1.8 ± 0.7 mSv). Sensitivity was significantly higher for larger nodule diameter, lower BMI patients, lower image noise and for solid and calcified nodules (15).

Neroladaki and al. showed the same number of detected nodules between an ULD acquisition (0.16±0.006mSv) with iterative reconstruction and a standard dose filtered back projection acquisition (11.2±2.7mSv), and more nodules detected with model based iterative reconstruction (MBIR) than adaptive statistical iterative reconstruction (ASIR) (16). MBIR is known to better minimize image noise compared to ASIR : Ichikawa and al found a significantly lower image noise with LD (1.6 ± 0.8 mSv) MBIR CT (11.6 ± 1.0 Hounsfield units (HU)) than with LD ASIR CT (21.1 ± 2.6 HU, $p < 0.0005$), a slightly better image quality score for decreased lung attenuation lesion, and no difference in image quality scores for consolidation or mass, ground-glass attenuation, or reticular opacity with MBIR compared to ASIR LD CT (8). But MBIR may slightly deteriorate lesion margin (9), and significantly increases reconstruction time, taking more than 30 minutes, when patients lie less than 10 minutes in the machine. ASIR-V is the latest generation of hybrid iterative reconstruction (GE medical Healthcare, Milwaukee, WI). It combines ASIR and MBIR and enables a better noise reduction than ASIR, with a processing time of only few minutes, suitable to a routine chest CT session (17).

According to the ALARA (as low as reasonably achievable) principle, we hope to validate our ULD chest CT protocol (<0.2mSv), the dose of which is 10 times lower than a usual LD CT, as a sensitive

tool to detect lung nodules. Thus, this ULD CT acquisition could be generalized for lung nodules detection and would consolidate the setup of lung cancer screening programs. Also, this would allow the generalization of ULD protocols, for radiation sensitive populations (children and young adults in particular).

METHODS AND ANALYSIS

Study design and objectives

The objectives of this study are to evaluate the performance of ULD CT for the detection of lung nodules, and the evaluation of nodule characteristics in comparison to LD CT. Furthermore**,** as smoking is a common risk factor, performance for the detection of cardiac and respiratory associated diseases (bronchial abnormalities, emphysema, coronary calcifications) is also evaluated.

An additional ULD CT is performed in patients referred for non-enhanced chest CT for lung nodules check-up or follow-up. The dose delivered with both acquisitions is still lower than the French diagnostic reference level (6.65mSv). We chose to only include nodules ≥ 4mm as the incidence of cancer is very low below this threshold, and are not currently considered as clinically significant (18). Nodules < 3mm are considered as micronodules and the recommendation from the Fleischner Society recommends that such nodules should not be measured, given inherent accuracy limitations and variability in determining whether the lesion is a solid, part-solid, or ground-glass nodule (19). A 4 mm threshold was also used for the NLST study (2). In addition, fully calcified nodules are excluded from the analysis because they are constantly benign and easily detected.

We will study nodule subtypes (solid, part-solid and pure ground-glass) and size. Furthermore we will evaluate the performance of ULD CT to diagnose intrapulmonary lymph nodes, which are benign nodules not needing follow up (20), and were not analyzed in previous ULD CT studies.

This trial sponsored by the Grenoble-Alpes University Hospital (CHUGA, France) is designed as a monocentric, prospective, non-randomized study in which the patient is his own control. All outcomes are evaluated by blinded double reading. Patient enrollment started in October 2017 and is

expected to be completed in September 2018. Figure 1 summarizes the process of inclusion, intervention and reading, described in detail below.

Primary outcome

Detection rate (sensitivity) of lung nodules in ULD chest CT using the conventional chest LD CT as gold-standard.

Secondary outcomes

1) Diagnostic criteria: true positive (TP), false positive (FP), true negative (TN), false negative (FN), positive predictive value (PPV), negative predictive value (NPV), Specificity (Sp) of ULD CT

2) Concordance of nodule's size, subtype, and diagnosis of typical intrapulmonary lymph node among lung nodules between ULD and LD CT

3) Inter-observer reproducibility for size, subtype and diagnosis of lung nodules in ULD CT

4) Influence of subjects characteristics (age, sex, BMI), nodule location, and nodule size on lung nodule detection with ULD CT

5) Concordance of emphysema detection, type and distribution between ULD and LD CT

6) Concordance of Weston score of coronary calcifications between ULD and LD CT

7) Concordance of visual assessment of bronchial thickening, mucoid impaction or dilatation between ULD and LD CT

Eligibility Criteria

Inclusion criteria

- aged 18 years or older
- referred for non-enhanced chest CT for the following indications:
  - lung nodule check-up or follow-up
  - nodular abnormality on chest X ray
  - morphologic assessment of chronic obstructive pulmonary disease (COPD) or emphysema

- asbestos exposure
- assessment before lung radio frequency ablation
- assessment of disease extent of an extra thoracic cancer (in case of iodinated intravenous contrast agent contraindication)
- Check-up before extra-thoracic transplantation (in case of iodinated intravenous contrast agent contraindication).

Exclusion criteria

- Inability to lie down and stay still during the examination
- Inability to hold breath for more than 5 seconds
- Pneumonia in the last 3 months
- Body mass index (BMI) more than 35kg/m²
- Pregnant or breastfeeding women

CT scan acquisitions and reconstructions

The LD and ULD acquisitions are performed on the Revolution CT scanner (GE medical Healthcare, Milwaukee, WI, USA) equipped with the third generation ASIR-V iterative reconstruction. Acquisitions are performed successively in the same CT exam, in the supine position and at suspended full inspiration. Both acquisitions cover the same pulmonary fields from the apex to the costo-diaphragmatic angle, determined on the scout views (2 views).

The LD acquisition is the reference exam for the diagnosis of pulmonary nodules. The acquisition parameters are: spiral CT scanning; 120kVp; automatic modulation of 3D radiation dose ("Smart mA"+ Organ Dose Modulation) with lower bound 100mA, maximal bound 200mA and noise index 10; rotation time: 0.35sec ; modulation 35-70 mAs; pitch = 0.992 :1 and collimation: 80mm. The radiation dose, CTDIvol (volume CT dose index) and DLP (Dose Length Product = CTDIvol x length of exposure) may vary depending on patient attenuation and length of the acquisition. The expected

DLP is between 70 and 200mGy.cm (0.98mSv to 2.8mSv) (the effective dose is calculated by multiplying DLP by a thoracic conversion factor of 0.014 (21)), for an average DLP of 100mGy.cm. The ULD CT acquisition parameters are: spiral CT scanning; 120kVp; fixed tube current of 10mA; rotation time: 0.35s; 3.5 mAs; pitch: 0.992 :1, collimation: 80mm. These parameters are fixed for all patients. The CTDIvol is constant at 0.24mGy. The DLP will depend only on the length of the acquired chest, different for each patient, expected around 10mGy.cm (0.14mSv). The modulation of the mA is deactivated to allow a very low tube current and therefore an ULD acquisition. The ULD acquisition increases the exam time by up to two minutes.

The reconstruction parameters are identical for both acquisitions: slice thickness: 1.25mm; standard filter and lung filter; contiguous 8-mm thickness Maximal Intensity projection (MIP) reconstruction, and iterative reconstruction with different percentages. We use ASIR-V in our study which is the latest generation of iterative reconstruction techniques. It blends hybrid iterative reconstruction and standard filtered back projection. The percentage of ASIR-V represents the amount of iterative reconstruction, from 0% (filtered back projection only) to 100% iterative reconstruction, which modifies image noise and texture. When designing our study, ASIR-V was not yet studied for chest CT. The CT vendor engineers suggested an empirical percentage between 40 up to 100%, depending on radiologist practice and preferences. We decided to test percentages of iterative reconstruction of 50% and 100%. The LD CT images are reconstructed with 50% ASIR-V (LD) and the ULD CT images with 50% (ULD50) and 100% (ULD100) ASIR-V.

The statistical analyses will be performed twice: with ULD50 and ULD100.

For every patient, CTDIvol and DLP are recorded. Effective dose and Size Specific Dose Estimates (SSDE) will be then calculated. Concerning the additional radiation for included patients, our ULD CT protocol has an expected effective dose between 0.10 and 0.20 mSv, which is about 6 to 20 times lower than the LD protocol (which is the usual dose in our institution for this indication), similar to a 2-views CXR, and to 30 days of natural radiation (22). Moreover, total dose of the entire exam (around 1.1 to 3 mSv) is lower than French diagnostic reference level of 6.65mSv.

Recruitment and intervention

Patients included in the study are those referred for a diagnostic chest CT without contrast media injection. On the day of the CT scan, a radiologist checks the eligibility criteria for the study, and informs the patient who signs a participation consent form if he accepts to join the study. The radiologist then collects the following parameters: height, weight, history of oncology, cardio-respiratory pathology and exposure to smoking. The patient then undergoes the standard diagnostic LD CT acquisition followed by the ULD acquisition. If, however, the dose of the LD acquisition is greater than 6.65mSv (French diagnostic reference level), the ULD acquisition is not performed and the patient is excluded from the data analysis. The patient's participation in the study is completed once he leaves the examination room.

The CT images of the LD acquisition are analysed by the radiologist who gives his medical report for the patient's medical management. If the number of nodules ≥ 4 mm identified on this acquisition is ≥6 in one lung, the patient will be excluded from the data analysis because the analysis of the outcomes will be too complicated to implement.

Patient and Public Involvement

Patients or public were not directly involved in the development of the research question. However, lowering the radiation dose is a rising concern for the patients and for public health. Patients were also not directly involved in the design, the recruitment and the conduct of this study.

As a regular medical care, the report of the diagnostic LD CT is sent to the prescribing physician, and to the patients at their request. According to French law, patients will be informed of the global results of the study at their request.

Blind reading of outcomes

For LD, ULD50 and ULD100 reconstructions, 2 radiologists will independently read all the radiological parameters. In order to limit the number of exams assessed by each reader, 4 radiologists

split into 2 pairs will participate in the blind reading. Each pair of radiologists (1 junior and 1 senior radiologist) reads the three sets of images for the same patient in a random order.

The term “blind” means that radiologists have neither knowledge of the patient's identity nor access to the results of diagnostic reading. To avoid patient identification, CT acquisitions are anonymized by deleting in the DICOM fields: the name, age and date of birth of the patient; the date and time of the examination and the name of the referring radiologist for the diagnosis. Each patient reconstruction is identified by a random number that differs for each of the two readers. Radiologists never read two series of the same patient consecutively.

Anonymized exams are periodically transmitted to a pair with at least 15 LD, 15 ULD50 and 15 ULD100 reconstructions. The three patient reconstructions are not necessarily given the same day to both radiologists. In addition, the order of presentation is not identical for the two radiologists.

The reading is performed on a diagnostic console (IMPAX software, 6.5.5.3502) (Agfa, Belgium) using Barco MDNC-3121monitors (Barco, Courtrai, Belgium) and includes mediastinal and parenchymal filter reconstructions for each acquisition. The radiologist is free to adapt the level and width of the window to its reading practice (initial parenchymal window defined by a width of 1500UH and a level of -600UH), and to perform multiplanar reconstructions in the different plans of space. The reading also includes the additional MIP reconstruction for each acquisition, in order to sensitize the detection of nodules (23) (this type of reading from MIP series is performed in clinical routine).

Radiologists identify nodules of longer diameter ≥4mm by locating them with the slice number and the lobe. It is known that each lung has three lobes (right upper lobe, middle lobe, right lower lobe, culmen, lingula, and left lower lobe). Each radiologist completes a reading grid for each reconstruction with all detected nodule characteristics, evaluation of emphysema, coronary calcification and bronchial abnormalities.

The completed grids are given to a Clinical Research Assistant for data entry and identification of discrepancies in identification of nodules between the two radiologists.

We consider that a nodule is the same between the two readers if:

- it is located in the same lobe
- the slice number is identical at ± 5 slices (a nodule will be visible on several successive slices)
- the longest diameter of nodule is the same at ± 2mm (24)

If these criteria are not respected or if a radiologist identifies one or more nodules in addition to or less than the second radiologist, a consensus with a third CHUGA senior thoracic radiologist with 27 years of experience is obtained. This third radiologist is not part of the reading pairs. The consensus is made from anonymized reconstructions and the reconstructions of the same patient are not processed successively.

Besides, for every reconstruction is recorded:

- noise by measuring standard deviation in a region of interest placed in the tracheal air above the carina,
- shape of the trachea which indicates inspiration degree,
- subjective image quality on a 3-point scale.

Data monitoring

All data is monitored by Grenoble-Alpes University Hospital (trial sponsor), in order to verify that for every patient enrolled there is a signed consent form and that the inclusion and exclusion criteria are respected. In addition all data collected in the case report form of every enrolled patient are verified.

Sample size

With a 90% power, to have a sensitivity of detection of nodules with the ULD CT to 90% with a confidence interval to ±10%, it would be necessary to analyze 124 nodules. According to a retrospective analysis of patients with indication of pulmonary nodule CT made at CHUGA, out of 420 patients per year with this indication, 210 present pulmonary nodules with a total of about 400

nodules. It should therefore include about 140 patients to have 124 nodules to be analyzed. Considering a 5% potential loss to follow-up or withdrawal of consent, the actual number of subjects to include is 147 in total. To this are added three potential patients who could be secondarily excluded from the study for a number of nodules ≥6 in one of the lungs. The total number of patients to include is 150. The sample size calculations were carried out using R software version 3.1.0 (library MKmisc, function power.diagnostic.test) (25, 26, 27).

Statistical analysis

In this non-randomized study where each patient is his own control, the threshold $p<0.05$ will be taken into account to define the significance of the statistical tests. Analyses will be carried out in accordance with good statistical analysis practices after freezing of the database and will be carried out with the software R (version ≥ 3.1.0).

The normality of the quantitative parameters will be determined by the Shapiro-Wilks test or by graphical verification of the symmetry of the distribution. When the normality of the distribution of such a parameter has been demonstrated, it will be described by its mean and its standard deviation. Otherwise it will be described by its median, the 25th and the 75th percentile. The qualitative parameters will be expressed in number and percentage.

For the main objective, the sensitivity of the ULD CT (compared to the LD CT) for the detection of nodules will be calculated and accompanied by a 95% confidence interval. For secondary objective 1, the number of TP, FP, TN, FN, PPV, NPV and Sp of the ULD CT (compared to LD CT) will be calculated. For secondary objectives 2, 5, 6 and 7, the concordance of the qualitative variables will be evaluated using the kappa coefficient. The concordance of the quantitative variables will be evaluated using Lin's concordance coefficient. For each coefficient, the 95% confidence interval will be given. For secondary objective 3, inter-observer reproducibility for qualitative variables will be evaluated using the kappa coefficient. It will be evaluated, for the quantitative variables, using the ICC (intra class coefficient). For each coefficient, the 95% confidence interval will be given. For

secondary objective 4, a logistic regression model will be implemented. The variable to be explained will be the result of detecting each nodule in ULD CT compared to the LD CT (0 = good detection / 1 = bad detection). The explanatory variables will be the age, sex and BMI of the patient, the location (lobe) and the size of the nodule. The size of the nodule can be used as a qualitative variable (<5mm, 5-10mm,> 10mm).

An interim analysis including the analysis of the primary endpoint will be performed after inclusion of the first 50 patients. This interim analysis will aim to: decide whether to continue or stop the study for futility and readjust the number of patients if necessary (if the characteristics of the patients included do not correspond to those initially planned (too many patients without nodules ≥4 mm)). In order to maintain an overall threshold of 5% in the final analysis, the interim analysis will be carried out with a threshold of 0.1%. The results of the interim analysis will be taken into account by the steering committee to propose modifications to the analysis plan. For this interim analysis, data from the confrontation between the two radiologists will be used.

Limitations

First limitation of our protocol is that we do not have a true screening population because there is no organized lung cancer screening program in our country yet. Therefore, our study population corresponds to patients routinely referred for lung nodule checkup or follow up instead of a risk-factor based population.

Another limitation is that ULD CT is easily recognizable as the image noise is increased as compared to LD CT, as well as ULD 50 and ULD 100 are possible to distinguish for an experienced radiologist. As a consequence, readers were not blinded for these, but for patient name, sex, age, clinical status, and CT report.

Recall bias is limited by a randomized order of presentation and cutting into several reading sessions.

Although we wanted to have a "western population", we decided not to include obese patients with a BMI>35, because ULD CT are of poorer quality, due to the need of more radiation-exposure to

produce acceptable images. Vardhanabhuti and al. recently found a loss of nodule detection with iterative reconstructed CT scanners at an effective dose of 0.14±0.01mSv for obese patients with BMI>38 (28).

We decided to test percentage of 50 and 100% of ASIR-V. Tang and al. tested ASIR-V from 10 to 100% in non-enhanced chest and showed ASIR-V has greater potential in reducing image noise and artifacts and maintaining image sharpness when compared to ASIR, and 60% ASIR-V had the highest image quality combining both the objective and subjective evaluation of images (29). This finding, although occurring after the design of our study is close to our chosen 50% level of ASIR-V.

Finally, our study has been conceived before the recommendations of the EU Position statement published at the end of 2017(30). Therefore, we measured manually the nodules instead of using computerized volumetry.

FUNDING

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AUTHOR CONTRIBUTIONS

M. Ludwig is the corresponding author and contributed to the conception of the study, to the inclusion of patients, to the blind reading of outcomes and to the drafting of the manuscript.

E. Chipon contributed to the conception of the study, to the drafting of the manuscript, and is responsible for data management and its integrity.

J. Cohen contributed to the conception of the study, to the inclusion of patients, to the blind reading of outcomes and to the revision of the manuscript.

E. Reymond contributed to the inclusion of patients, to the blind reading of outcomes and to the revision of the manuscript.

M. Medici contributed to the design and application of statistical analysis, and to the drafting of the manuscript.

A. Cole contributed to the blind reading of outcomes and to the revision of the manuscript.

A. Moreau Gaudry contributed to the conception of the study and to the revision of the manuscript.

G R Ferretti is the principal investigator of the study and contributed to the conception of the work, to the inclusion of patients, to the blind consensus of outcomes and to the revision of the manuscript.

All authors approved the final manuscript and agreed to be accountable for all aspects of the work.

COMPETING INTERESTS

The authors declare that they have no competing interests

CONSENT FOR PUBLICATION

Not applicable

ETHICS AND DISSEMINATION

This trial is registered on the ClinicalTrials.gov database (reference NCT03305978) (see supplementary file "trial registration data set"), and was approved by the relevant ethical committee (Comité de Protection des Personnes, CPP sud-est VI, France, 07/07/2017, CPP Reference: AU1342). The Protocol version is N°1.0- Date: May 4th 2017

All patients sign a consent form before being enrolled in the trial, in accordance with the Declaration of Helsinki II.

Once the statistical report is finalized, we plan to publish our results in an international scientific journal and present them in national and international congresses.

DATA STATEMENT

Legal restrictions (French personal data laws) prohibit the authors from making the minimal data set publicly available. These data are available upon request.

ACKNOWLEDGEMENTS

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REFERENCES

1. Globocan : Lung Cancer Estimated Incidence, Mortality and Prevalence Worldwide in 2012 http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx)
2. National Lung Screening Trial Research Team, Denise R. Aberle, Amanda M. Adams, Christine D. Berg, William C. Black, Jonathan D. Clapp, Richard M. Fagerstrom, et al. "Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening." *The New England Journal of Medicine* 365, no. 5 (August 4, 2011): 395–409. doi:10.1056/NEJMoa1102873
3. Yousaf-Khan U, van der Aalst C, de Jong PA, et al."Final screening round of the NELSON lung cancer screening trial: the effect of a 2.5-year screening interval." Thorax 2017;72:48-56. 10.1136/thoraxjnl-2016-208655
4. Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation and National Research Council. Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2.Washington, D.C: The National Academies Press; 2006

5. Kubo T, Ohno Y, Seo JB, Yamashiro T, Kalender WA, Lee CH, et al. "Securing safe and informative thoracic CT examinations-Progress of radiation dose reduction techniques". Eur J Radiol. 2017 Jan;86:313–9.

6. Kim, Yookyung, Yoon Kyung Kim, Bo Eun Lee, SeokJeong Lee, YonJuRyu, Jin Hwa Lee, and Jung Hyun Chang. "Ultra-Low-Dose CT of the Thorax Using Iterative Reconstruction: Evaluation of Image Quality and Radiation Dose Reduction." *AJR. American Journal of Roentgenology* 204, no. 6 (June 2015): 1197–1202. doi:10.2214/AJR.14.13629.

7. Vardhanabhuti, Varut, Robert J. Loader, Grant R. Mitchell, Richard D. Riordan, and Carl A. Roobottom. "Image Quality Assessment of Standard- and Low-Dose Chest CT Using Filtered Back Projection, Adaptive Statistical Iterative Reconstruction, and Novel Model-Based Iterative Reconstruction Algorithms." *AJR. American Journal of Roentgenology* 200, no. 3 (March 2013): 545–52. doi:10.2214/AJR.12.9424.

8. Ichikawa, Yasutaka, Kakuya Kitagawa, Naoki Nagasawa, Shuichi Murashima, and Hajime Sakuma. "CT of the Chest with Model-Based, Fully Iterative Reconstruction: Comparison with Adaptive Statistical Iterative Reconstruction." *BMC Medical Imaging* 13 (2013): 27. doi:10.1186/1471-2342-13-27.

9. Padole, Atul, Sarabjeet Singh, Jeanne B. Ackman, Carol Wu, Synho Do, Sarvenaz Pourjabbar, Ranish Deedar Ali Khawaja, et al. "Submillisievert Chest CT with Filtered Back Projection and Iterative Reconstruction Techniques." *AJR. American Journal of Roentgenology* 203, no. 4 (October 2014): 772–81. doi:10.2214/AJR.13.12312.

10. Montet, Xavier, Anne-Lise Hachulla, Angeliki Neroladaki, Frederic Lador, Thierry Rochat, Diomidis Botsikas, and Christoph D. Becker. "Image Quality of Low mA CT Pulmonary Angiography Reconstructed with Model Based Iterative Reconstruction versus Standard CT Pulmonary Angiography Reconstructed with Filtered Back Projection: An Equivalency Trial." *EuropeanRadiology* 25, no. 6 (June 2015): 1665–71. doi:10.1007/s00330-014-3563-5.

11. Yoon, Hyun Jung, Myung Jin Chung, Hye Sun Hwang, Jung Won Moon, and Kyung Soo Lee. "Adaptive Statistical Iterative Reconstruction-Applied Ultra-Low-Dose CT with Radiography-Comparable Radiation Dose: Usefulness for Lung Nodule Detection." *Korean Journal of Radiology* 16, no. 5 (October 2015): 1132–41. doi:10.3348/kjr.2015.16.5.1132

12. Sui, Xin, Felix G. Meinel, Wei Song, Xiaoli Xu, Zixing Wang, Yuyan Wang, Zhengyu Jin, Jiuhong Chen, Rozemarijn Vliegenthart, and U. Joseph Schoepf. "Detection and Size Measurements of Pulmonary Nodules in Ultra-Low-Dose CT with Iterative Reconstruction Compared to Low Dose CT." *European Journal of Radiology* 85, no. 3 (March 2016): 564–70. doi:10.1016/j.ejrad.2015.12.013

13. Nagatani Y, Takahashi M, Murata K, Ikeda M, Yamashiro T, Miyara T, Koyama H, Koyama M, Sato Y, Moriya H, et al "Lung nodule detection performance in five observers on computed tomography (CT) with adaptive iterative dose reduction using three-dimensional processing (AIDR 3D) in a Japanese multicenter study: Comparison between ultra-low-dose CT and low-dose CT by receiver-operating characteristic analysis".*Eur J Radiol. 2015 Jul; 84(7):1401-12. Epub 2015 Apr 2*

14. Huber, Adrian, Julia Landau, Lukas Ebner, Yanik Bütikofer, Lars Leidolt, Barbara Brela, Michelle May, Johannes Heverhagen, and Andreas Christe. "Performance of Ultralow-Dose CT with Iterative Reconstruction in Lung Cancer Screening: Limiting Radiation Exposure to the Equivalent of Conventional Chest X-Ray Imaging." *EuropeanRadiology*, January 26, 2016. doi:10.1007/s00330-015-4192-3

15. Messerli M, Kluckert T, Knitel M, Wälti S, Desbiolles L, Rengier F, et al. "Ultralow dose CT for pulmonary nodule detection with chest x-ray equivalent dose - a prospective intra-individual comparative study". EurRadiol. 2017 Aug;27(8):3290–9.

16. Neroladaki, Angeliki, Diomidis Botsikas, Sana Boudabbous, Christoph D. Becker, and Xavier Montet. "Computed Tomography of the Chest with Model-Based Iterative Reconstruction

Using a Radiation Exposure Similar to Chest X-Ray Examination: Preliminary Observations." *EuropeanRadiology* 23, no. 2 (February 2013): 360–66. doi:10.1007/s00330-012-2627-7.

17. De Marco P, Origgi D. "New adaptive statistical iterative reconstruction ASiR-V: Assessment of noise performance in comparison to ASiR". J Appl Clin Med Phys. 2018 Mar;19(2):275-286. doi: 10.1002/acm2.12253. Epub 2018 Jan 24. PubMed PMID: 29363260; PubMed Central PMCID: PMC5849834
18. Gierada DS, Pinsky P, Nath H, Chiles C, Duan F, Aberle DR. "Projected outcomes using different nodule sizes to define a positive CT lung cancer screening examination". J Natl Cancer Inst. 2014;106:dju284
19. Bankier A, MacMahon H, Goo JM, et al. Recommendations for Measuring Pulmonary Nodules at CT: A Statement from the Fleischner Society. Radiology 2017;285:584-600 doi:10.1148/radiol.2017162894
20. Ahn MI, Gleeson TG, Chan IH et-al. "Perifissural nodules seen at CT screening for lung cancer". Radiology. 2010;254 (3): 949-56. doi:10.1148/radiol.09090031
21. Task Group on Control of Radiation Dose in Computed Tomography. "Managing Patient Dose in Computed Tomography. A Report of the International Commission on Radiological Protection." *Annals of the ICRP* 30, no. 4 (2000): 7–45
22. Exposition de la population française aux rayonnements ionisants liée aux actes de diagnostic médical en 2012. Rapport IRSN PRP-HOM N°2014-6
23. Jankowski, A., T. Martinelli, J. F. Timsit, C. Brambilla, F. Thony, M. Coulomb, and G. Ferretti. "Pulmonary Nodule Detection on MDCT Images: Evaluation of Diagnostic Performance Using Thin Axial Images, Maximum Intensity Projections, and Computer-Assisted Detection." European Radiology 17, no. 12 (December 2007): 3148–56. doi:10.1007/s00330-007-0727-6.

24. Revel MP, Bissery A, Bienvenu M, Aycard L, Lefort C, Frija G. Are two-dimensional CT measurements of small noncalcified pulmonary nodules reliable? Radiology. 2004 May;231(2):453-8. PubMed PMID: 15128990.

25. A. Flahault, M. Cadilhac, and G. Thomas (2005). Sample size calculation should be performed for design accuracy in diagnostic test studies. Journal of ClinicalEpidemiology, 58(8):859-862.

26. H. Chu and S.R. Cole (2007). Sample size calculation using exact methods in diagnostic test studies. Journal of ClinicalEpidemiology, 60(11):1201-1202.

27. M.R. Chernickamd C.Y. Liu (2002). The saw-toothed behavior of power versus sample size and software solutions: single binomial proportion using exact methods. Am Stat, 56:149-155.

28. Vardhanabhuti V, Pang CL, Tenant S, Taylor J, Hyde C, Roobottom C. "Prospective intra-individual comparison of standard dose versus reduced-dose thoracic CT using hybrid and pure iterative reconstruction in a follow-up cohort of pulmonary nodules-Effect of detectability of pulmonary nodules with lowering dose based on nodule size, type and body mass index". Eur J Radiol. 2017 Jun;91:130-141. doi: 10.1016/j.ejrad.2017.04.006

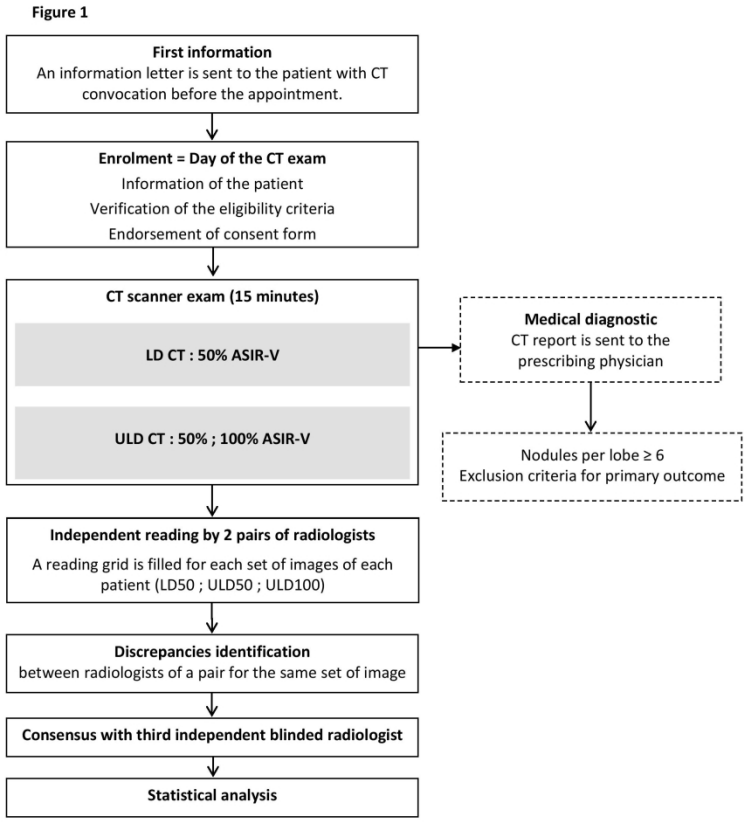
29. Tang H, Yu N, Jia Y, Yu Y, Duan H, Han D, et al. "Assessment of noise reduction potential and image quality improvement of a new generation adaptive statistical iterative reconstruction (ASIR-V) in chest CT". Br J Radiol. 2018 Jan;91(1081):20170521

30. Oudkerk M, Devaraj A, Vliegenthart R, et al. European position statement on lung cancer screening. Lancet Oncol 2017;18: e754–66. http://dx.doi.org/10.1016/S1470-2045(17)30861-6

FIGURE 1 legend:

Study Flow chart. ASIR-V ®, adaptive statistical iterative reconstruction-Véo (GE medical Healthcare, Milwaukee, WI, USA); CT, computed tomography; LD, low dose; LD50, low

dose CT with 50% ASIR-V reconstruction; ULD, ultra-low dose; ULD50, ultra-low dose CT with 50% ASIR-V reconstruction, ULD 100, ultra-low dose CT with 100% ASIR-V reconstruction



Study Flow chart. ASIR-V ®, adaptive statistical iterative reconstruction-Véo (GE medical Healthcare, Milwaukee, WI, USA); CT, computed tomography; LD, low dose; LD50, low dose CT with 50% ASIR-V reconstruction; ULD, ultra-low dose; ULD50, ultra-low dose CT with 50% ASIR-V reconstruction, ULD 100, ultra-low dose CT with 100% ASIR-V reconstruction.

210x297mm (300 x 300 DPI)

Trial registration data set :

Primary registry and trial identifying number	ClinicalTrials.gov NCT03305978
Date of registration in primary registry	September 26, 2017
Secondary identifying numbers	38RC17.132
Source(s) of monetary or material support	University Hospital, Grenoble
Primary sponsor	University Hospital, Grenoble
Secondary sponsor(s)	French Thoracic Imaging Society
Contact for public queries	Emilie CHIPON, PhD, +33476767313, echipon@chu-grenoble.fr
Contact for scientific queries	Gilbert FERRETTI, MD PhD, +3376767313, gferretti@chu-grenoble.fr
Public title	Pulmonary Nodule Detection: Comparison of an Ultra Low Dose vs Standard Scan.
Scientific title	Detection of Pulmonary Nodules: Comparison of Ultra-low-dose Chest CT (Approaching a Two Views Chest X-ray Radiation) and Standard Low Dose CT. A Monocentric, Prospective, Non-randomized, Comparative, Open-label Study With Blind Reading of the Judgment Criteria
Country of recruitment	France
Health condition(s) or problem(s) studied	Lung cancer screening, radiation exposure
Intervention(s)	Device: Ultra low dose chest CT An additional ultra low dose CT row is performed for every subject besides standard diagnostic low dose chest CT. Other Name: Revolution CT (GE Healthcare) 442507CN0, equiped with ASIR V
	Device: Low dose chest CT standard diagnostic low dose chest CT Other Name: Revolution CT (GE Healthcare)
Key inclusion and exclusion criteria	Ages eligible for study: ≥18 years Sexes eligible for study: both Accepts healthy volunteers: no
	Inclusion criteria : Patients referred for non enhanced chest CT for following indications : - lung nodule search or control - nodular abnormality on chest X ray - statement of COPD or emphysema - asbestos exposure - nodule localization before radio frequency ablation - assessment of disease extent of an extra thoracic cancer (in case of iodinated intravenous contrast agent contraindication) - statement before extrathoracic transplantation (in case of iodinated intravenous contrast agent contraindication) Affiliated with the french social security Who signed consent
	Exclusion criteria : Inability to lie down and stay still during the examination Inability to hold breath more than 5 seconds Pneumonia in the last 3 months Body mass index more than 35kg/m² exclusion period of another interventionnal study

	referred for articles L1121-5 to L1121-8 of french public health code Pregnant or breastfeeding women
Study type	Interventional
	Allocation: Non-Randomized Intervention Model: Sequential Assignment Intervention Model Description: Major Patient Addressed for Thoracic CT without Injection of Contrast Masking: Single (Outcomes Assessor) Masking Description: blinding evaluation of criteria
	Primary purpose: diagnostic
Date of first enrolment	October 3, 2017
Target sample size	150
Recruitment status	Recruiting
Primary outcome(s)	Ultra low dose CT lung nodule detection sensibility [Time Frame: 22 months] Detection rate (%) of ≥4mm lung nodules in ultra low dose chest CT versus standard low
Key secondary outcomes	- Ultra low dose CT diagnostic performances of lung nodule detection [Time Frame: 22 months] :true positives, false positives, true negatives, false negatives, positive predictive value, negative predictive value, specificity, of ≥4mm lung nodules detection within ultra low dose chest CT versus standard low dose chest CT - Concordance of ≥4mm lung nodules characteristics between ultra low dose and standard low dose chest CT [Time Frame: 22 months] : comparison of size, density, type (true nodule or intrapulmonary ganglion) of ≥4mm lung nodule between ultra low dose and standard low dose chest CT - Ultra low dose CT inter-observer reproducibility [Time Frame: 22 months] : inter observer reproducibility for size, density and type of ≥4mm lung nodule detected in ultra low dose CT - Influence of subjects characteristics, nodule location, and nodule size on detection between ultra low dose and standard low dose chest CT [Time Frame: 22 months] : analysis of subjects characteristics (age, gender, body mass index), ≥4mm nodule location, and ≥4 mm nodule size on detection between ultra low dose and standard low dose chest CT - Concordance of emphysema characteristics between ultra low dose and standard low dose chest CT [Time Frame: 22 months] : comparison of emphysema detection, type (centrilobular, paraseptal, panlobular, bullous) and distribution between ultra low dose and standard low dose chest CT - Concordance of coronary calcification detection and quantification between ultra low dose and standard low dose chest CT [Time Frame: 22 months] : Comparison of Weston scores between ultra low dose and standard low dose chest CT - Concordance of bronchial abnormalities evaluation between ultra low dose and standard low dose chest CT [Time Frame: 22 months] : comparison of detection of bronchial thickening or dilatation between ultra low dose and standard low dose chest CT
Ethics Review	approved by the relevant ethical committee (Comité de Protection des Personnes, CPP Sud-Est VI, France, CPP Reference: AU1342), on July 7, 2017

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	17
Protocol version	#3	Date and version identifier	18
Funding	#4	Sources and types of financial, material, and other support	16
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1;16
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	2

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6
Objectives	#7	Specific objectives or hypotheses	7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	11
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n/a
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	n/a

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	n/a
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	16
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	n/a
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Data access	#29	Statement of who will have access to the final trial dataset,	19

		and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

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Detection of pulmonary nodules: a clinical study protocol to compare ultra-low dose chest CT and standard low-dose CT using ASIR-V.

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Detection of pulmonary nodules: a clinical study protocol to compare ultra-low dose chest CT and standard low-dose CT using ASIR-V.

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ABSTRACT

Introduction:

Lung cancer screening in individuals at risk has been recommended by various scientific institutions. One of the main concerns for CT screening is repeated radiation exposure, with the risk of inducing malignancies in healthy individuals. Therefore, lowering the radiation dose is one of the main objectives for radiologists. The aim of this study is to demonstrate that an ultra-low dose (ULD) chest CT protocol, using recently introduced hybrid iterative reconstruction (ASiR-V, GE medical Healthcare, Milwaukee, WI, USA), is as performant as a standard "low dose" (LD) CT to detect non calcified lung nodules ≥ 4mm.

Methods and analysis:

The total number of patients to include is 150. Those are referred for non-enhanced chest CT for detection or follow-up of lung nodule and will undergo an additional unenhanced ULD CT acquisition, the dose of which is on average 10 times lower than the conventional LD acquisition. Total dose of the entire exam (LD + ULD) is lower than the French diagnostic reference level for a chest CT (6.65 milliSievert). ULD CT images will be reconstructed with 50% and 100% ASIR-V, and LD CT with 50%. The 3 sets of images will be read in random order by two pair of radiologists, in a blind test, where patient identification and study outcomes are concealed. Detection rate (sensitivity) is the primary outcome. Secondary outcomes will include concordance of nodule characteristics; inter-observer reproducibility; influence of subjects' characteristics, nodule location, and nodule size; and concordance of emphysema, coronary calcifications evaluated by visual scoring and bronchial alterations between LD and ULD CT. In case of discordance, a third radiologist will arbitrate.

Ethics and dissemination:

The study was approved by the relevant ethical committee. Each study participant will sign an informed consent form.

Trial registration number: *Clinicaltrials.gov* NCT03305978

ARTICLE SUMMARY:

STRENGTHS AND LIMITATIONS OF THIS STUDY

- We will evaluate the sensitivity of an ultra-low dose CT, delivering 10 times less radiation than conventional low-dose CT, to detect lung nodules, in a French population of 150 patients referred for lung nodule check-up or follow-up.
- We will use a recently introduced hybrid iterative reconstruction (ASiR-V) and different levels of ASIR-V will be assessed
- Nodules characteristics will be analyzed in particular the diagnosis of intrapulmonary lymph node, which is a benign lesion.
- Patients with morbid obesity (BMI>35) will not be included as image quality of ultra-low dose CT is not acceptable for those morphotypes.
- Readers will be aware of the type of CT acquisition (LD and ULD) and reconstruction, because they are easily recognizable due to the different level of image noise.

INTRODUCTION

Lung cancer is the deadliest cancer in the world (1), mainly due to the fact that it is often diagnosed at advanced stages that are not surgically curable. The current challenge is therefore to detect lung cancer at early asymptomatic stages. Risk factors such as smoking and occupational exposure (mainly asbestos, silica, arsenic, chromium, iron, coal, ionising radiation) are well known and enable to define the target population for such programs.

The National Lung Screening Trial (NLST) was the first study to show that a low dose (LD) (average effective dose of 1.5mSv) computed tomography (CT) lung cancer screening reduced specific death by 20% (95% CI, 6.8 to 26.7; P=0.004) as compared with chest X Ray (CXR) screening (single-view posteroanterior) in actual or former smokers (>30 pack years) patients between 55 and 74 years old (2).

Other lung cancer screening studies are still in progress in Europe, such as the NELSON study in Belgium and the Netherlands, the results of which are expected to be reported soon (3)

However, the drawback of using LD CT at such doses (<1.5 millisievert (mSv)) is that even though irradiating less than standard chest CT, the radiation exposure is still on average 10 times higher than a 2 views CXR, and may be a risk for induced malignancies in itself. (4)

In this context, great efforts are currently being made by CT manufacturers to reduce the dose and maintain diagnostic quality. Technologies such as automated exposure control, lower tube current and iterative reconstruction (5), were recently introduced, enabling further dose decrease for chest CTs, and the concept of “ultra-low dose (ULD) CT” (or submillisievert CT), which delivers a radiation dose approaching that of 2 CXR views at the cost of a slight deterioration of the image quality (6). Among these technological advances, the most significant is probably the new iterative reconstruction whether full iterative or hybrid. (7,8,9,10)

Promising results have been published for lung nodule detection with ULD CT (11,12,13). However, these studies were conducted on Asian populations, which may have different morphotypes compared to Caucasian populations.

Huber and al. performed a phantom study comparing standard, LD and ULD CT for detection of pulmonary nodules. When compared to standard CT, the detection rate was 95.5% for LD CT (1.76 mSv), and 93.3% for ULD CT (0.13mSv), increasing at 97.5% when adding computer aided diagnosis and maximal intensity projection (14).

Since we started to design our study protocol, Messerli and al. published a study including 202 patients referred for any clinically indicated chest CT. 91.2% nodules were detected using ULD CT (0.13+/-0.01mSv) as compared to LD CT (1.8 ± 0.7 mSv). Sensitivity was significantly higher for larger nodule diameter, lower BMI patients, lower image noise and for solid and calcified nodules (15).

Neroladaki and al. showed the same number of detected nodules between an ULD acquisition (0.16±0.006mSv) with iterative reconstruction and a standard dose filtered back projection acquisition (11.2±2.7mSv), and more nodules detected with model based iterative reconstruction (MBIR) than adaptive statistical iterative reconstruction (ASIR) (16). MBIR is known to better minimize image noise compared to ASIR : Ichikawa and al found a significantly lower image noise with LD (1.6 ± 0.8 mSv) MBIR CT (11.6 ± 1.0 Hounsfield units (HU)) than with LD ASIR CT (21.1 ± 2.6 HU, $p < 0.0005$), a slightly better image quality score for decreased lung attenuation lesion, and no difference in image quality scores for consolidation or mass, ground-glass attenuation, or reticular opacity with MBIR compared to ASIR LD CT (8). But MBIR may slightly deteriorate lesion margin (9), and significantly increases reconstruction time, taking more than 30 minutes, when patients lie less than 10 minutes in the machine. ASIR-V is the latest generation of hybrid iterative reconstruction (GE medical Healthcare, Milwaukee, WI). It combines ASIR and MBIR and enables a better noise reduction than ASIR, with a processing time of only few minutes, suitable to a routine chest CT session (17).

According to the ALARA (as low as reasonably achievable) principle, we hope to validate our ULD chest CT protocol (<0.2mSv), the dose of which is 10 times lower than a usual LD CT, as a sensitive

tool to detect lung nodules. Thus, this ULD CT acquisition could be generalized for lung nodules detection and would consolidate the setup of lung cancer screening programs. Also, this would allow the generalization of ULD protocols, for radiation sensitive populations (children and young adults in particular).

METHODS AND ANALYSIS

Study design and objectives

The objectives of this study are to evaluate the performance of ULD CT for the detection of lung nodules, and the evaluation of nodule characteristics in comparison to LD CT. Furthermore**,** as smoking is a common risk factor, performance for the detection of cardiac and respiratory associated diseases (bronchial abnormalities, emphysema, coronary calcifications) is also evaluated.

An additional ULD CT is performed in patients referred for non-enhanced chest CT for lung nodules check-up or follow-up. The dose delivered with both acquisitions is still lower than the French diagnostic reference level (6.65mSv). We chose to only include nodules ≥ 4mm as the incidence of cancer is very low below this threshold, and are not currently considered as clinically significant (18). Nodules < 3mm are considered as micronodules and the recommendation from the Fleischner Society recommends that such nodules should not be measured, given inherent accuracy limitations and variability in determining whether the lesion is a solid, part-solid, or ground-glass nodule (19). A 4 mm threshold was also used for the NLST study (2). In addition, fully calcified nodules are excluded from the analysis because they are constantly benign and easily detected.

We will study nodule subtypes (solid, part-solid and pure ground-glass) and size. Furthermore we will evaluate the performance of ULD CT to diagnose intrapulmonary lymph nodes, which are benign nodules not needing follow up (20), and were not analyzed in previous ULD CT studies.

This trial sponsored by the Grenoble-Alpes University Hospital (CHUGA, France) is designed as a monocentric, prospective, non-randomized study in which the patient is his own control. All outcomes are evaluated by blinded double reading. Patient enrollment started in October 2017 and is

expected to be completed in September 2018. Figure 1 summarizes the process of inclusion, intervention and reading, described in detail below.

Primary outcome

Detection rate (sensitivity) of lung nodules in ULD chest CT using the conventional chest LD CT as gold-standard.

Secondary outcomes

1) Diagnostic criteria: true positive (TP), false positive (FP), true negative (TN), false negative (FN), positive predictive value (PPV), negative predictive value (NPV), Specificity (Sp) of ULD CT

2) Concordance of nodule's size, subtype, and diagnosis of typical intrapulmonary lymph node among lung nodules between ULD and LD CT

3) Inter-observer reproducibility for size, subtype and diagnosis of lung nodules in ULD CT

4) Influence of subjects characteristics (age, sex, BMI), nodule location, and nodule size on lung nodule detection with ULD CT

5) Concordance of emphysema detection, type and distribution between ULD and LD CT

6) Concordance of Weston score of coronary calcifications between ULD and LD CT

7) Concordance of visual assessment of bronchial thickening, mucoid impaction or dilatation between ULD and LD CT

Eligibility Criteria

Inclusion criteria

- aged 18 years or older
- referred for non-enhanced chest CT for the following indications:
  - lung nodule check-up or follow-up
  - nodular abnormality on chest X ray
  - morphologic assessment of chronic obstructive pulmonary disease (COPD) or emphysema

- asbestos exposure
- assessment before lung radio frequency ablation
- assessment of disease extent of an extra thoracic cancer (in case of iodinated intravenous contrast agent contraindication)
- Check-up before extra-thoracic transplantation (in case of iodinated intravenous contrast agent contraindication).

Exclusion criteria

- Inability to lie down and stay still during the examination
- Inability to hold breath for more than 5 seconds
- Pneumonia in the last 3 months
- Body mass index (BMI) more than 35kg/m²
- Pregnant or breastfeeding women

CT scan acquisitions and reconstructions

The LD and ULD acquisitions are performed on the Revolution CT scanner (GE medical Healthcare, Milwaukee, WI, USA) equipped with the third generation ASIR-V iterative reconstruction. Acquisitions are performed successively in the same CT exam, in the supine position and at suspended full inspiration. Both acquisitions cover the same pulmonary fields from the apex to the costo-diaphragmatic angle, determined on the scout views (2 views).

The LD acquisition is the reference exam for the diagnosis of pulmonary nodules. The acquisition parameters are: spiral CT scanning; 120kVp; automatic modulation of 3D radiation dose ("Smart mA"+ Organ Dose Modulation) with lower bound 100mA, maximal bound 200mA and noise index 10; rotation time: 0.35sec ; modulation 35-70 mAs; pitch = 0.992 :1 and collimation: 80mm. The radiation dose, CTDIvol (volume CT dose index) and DLP (Dose Length Product = CTDIvol x length of exposure) may vary depending on patient attenuation and length of the acquisition. The expected

DLP is between 70 and 200mGy.cm (0.98mSv to 2.8mSv) (the effective dose is calculated by multiplying DLP by a thoracic conversion factor of 0.014 (21)), for an average DLP of 100mGy.cm. The ULD CT acquisition parameters are: spiral CT scanning; 120kVp; fixed tube current of 10mA; rotation time: 0.35s; 3.5 mAs; pitch: 0.992 :1, collimation: 80mm. These parameters are fixed for all patients. The CTDIvol is constant at 0.24mGy. The DLP will depend only on the length of the acquired chest, different for each patient, expected around 10mGy.cm (0.14mSv). The modulation of the mA is deactivated to allow a very low tube current and therefore an ULD acquisition. The ULD acquisition increases the exam time by up to two minutes.

The reconstruction parameters are identical for both acquisitions: slice thickness: 1.25mm; standard filter and lung filter; contiguous 8-mm thickness Maximal Intensity projection (MIP) reconstruction, and iterative reconstruction with different percentages. We use ASIR-V in our study which is the latest generation of iterative reconstruction techniques. It blends hybrid iterative reconstruction and standard filtered back projection. The percentage of ASIR-V represents the amount of iterative reconstruction, from 0% (filtered back projection only) to 100% iterative reconstruction, which modifies image noise and texture. When designing our study, ASIR-V was not yet studied for chest CT. The CT vendor engineers suggested an empirical percentage between 40 up to 100%, depending on radiologist practice and preferences. We decided to test percentages of iterative reconstruction of 50% and 100%. The LD CT images are reconstructed with 50% ASIR-V (LD) and the ULD CT images with 50% (ULD50) and 100% (ULD100) ASIR-V.

The statistical analyses will be performed twice: with ULD50 and ULD100.

For every patient, CTDIvol and DLP are recorded. Effective dose and Size Specific Dose Estimates (SSDE) will be then calculated. Concerning the additional radiation for included patients, our ULD CT protocol has an expected effective dose between 0.10 and 0.20 mSv, which is about 6 to 20 times lower than the LD protocol (which is the usual dose in our institution for this indication), similar to a 2-views CXR, and to 30 days of natural radiation (22). Moreover, total dose of the entire exam (around 1.1 to 3 mSv) is lower than French diagnostic reference level of 6.65mSv.

Recruitment and intervention

Patients included in the study are those referred for a diagnostic chest CT without contrast media injection. On the day of the CT scan, a radiologist checks the eligibility criteria for the study, and informs the patient who signs a participation consent form if he accepts to join the study. The radiologist then collects the following parameters: height, weight, history of oncology, cardio-respiratory pathology and exposure to smoking. The patient then undergoes the standard diagnostic LD CT acquisition followed by the ULD acquisition. If, however, the dose of the LD acquisition is greater than 6.65mSv (French diagnostic reference level), the ULD acquisition is not performed and the patient is excluded from the data analysis. The patient's participation in the study is completed once he leaves the examination room.

The CT images of the LD acquisition are analysed by the radiologist who gives his medical report for the patient's medical management. If the number of nodules ≥ 4 mm identified on this acquisition is ≥6 in one lung, the patient will be excluded from the data analysis because the analysis of the outcomes will be too complicated to implement.

Patient and Public Involvement

Patients or public were not directly involved in the development of the research question. However, lowering the radiation dose is a rising concern for the patients and for public health. Patients were also not directly involved in the design, the recruitment and the conduct of this study.

As a regular medical care, the report of the diagnostic LD CT is sent to the prescribing physician, and to the patients at their request. According to French law, patients will be informed of the global results of the study at their request.

Blind reading of outcomes

For LD, ULD50 and ULD100 reconstructions, 2 radiologists will independently read all the radiological parameters. In order to limit the number of exams assessed by each reader, 4 radiologists

split into 2 pairs will participate in the blind reading. Each pair of radiologists (1 junior and 1 senior radiologist) reads the three sets of images for the same patient in a random order.

The term “blind” means that radiologists have neither knowledge of the patient's identity nor access to the results of diagnostic reading. To avoid patient identification, CT acquisitions are anonymized by deleting in the DICOM fields: the name, age and date of birth of the patient; the date and time of the examination and the name of the referring radiologist for the diagnosis. Each patient reconstruction is identified by a random number that differs for each of the two readers. Radiologists never read two series of the same patient consecutively.

Anonymized exams are periodically transmitted to a pair with at least 15 LD, 15 ULD50 and 15 ULD100 reconstructions. The three patient reconstructions are not necessarily given the same day to both radiologists. In addition, the order of presentation is not identical for the two radiologists.

The reading is performed on a diagnostic console (IMPAX software, 6.5.5.3502) (Agfa, Belgium) using Barco MDNC-3121monitors (Barco, Courtrai, Belgium) and includes mediastinal and parenchymal filter reconstructions for each acquisition. The radiologist is free to adapt the level and width of the window to its reading practice (initial parenchymal window defined by a width of 1500UH and a level of -600UH), and to perform multiplanar reconstructions in the different plans of space. The reading also includes the additional MIP reconstruction for each acquisition, in order to sensitize the detection of nodules (23) (this type of reading from MIP series is performed in clinical routine).

Radiologists identify nodules of longer diameter ≥4mm by locating them with the slice number and the lobe. It is known that each lung has three lobes (right upper lobe, middle lobe, right lower lobe, culmen, lingula, and left lower lobe). Each radiologist completes a reading grid for each reconstruction with all detected nodule characteristics, evaluation of emphysema, coronary calcification and bronchial abnormalities.

The completed grids are given to a Clinical Research Assistant for data entry and identification of discrepancies in identification of nodules between the two radiologists.

We consider that a nodule is the same between the two readers if:

- it is located in the same lobe
- the slice number is identical at ± 5 slices (a nodule will be visible on several successive slices)
- the longest diameter of nodule is the same at ± 2mm (24)

If these criteria are not respected or if a radiologist identifies one or more nodules in addition to or less than the second radiologist, a consensus with a third CHUGA senior thoracic radiologist with 27 years of experience is obtained. This third radiologist is not part of the reading pairs. The consensus is made from anonymized reconstructions and the reconstructions of the same patient are not processed successively.

Besides, for every reconstruction is recorded:

- noise by measuring standard deviation in a region of interest placed in the tracheal air above the carina,
- shape of the trachea which indicates inspiration degree,
- subjective image quality on a 3-point scale.

Data monitoring

All data is monitored by Grenoble-Alpes University Hospital (trial sponsor), in order to verify that for every patient enrolled there is a signed consent form and that the inclusion and exclusion criteria are respected. In addition all data collected in the case report form of every enrolled patient are verified.

Sample size

With a 90% power, to have a sensitivity of detection of nodules with the ULD CT to 90% with a confidence interval to ±10%, it would be necessary to analyze 124 nodules. According to a retrospective analysis of patients with indication of pulmonary nodule CT made at CHUGA, out of 420 patients per year with this indication, 210 present pulmonary nodules with a total of about 400

nodules. It should therefore include about 140 patients to have 124 nodules to be analyzed. Considering a 5% potential loss to follow-up or withdrawal of consent, the actual number of subjects to include is 147 in total. To this are added three potential patients who could be secondarily excluded from the study for a number of nodules ≥6 in one of the lungs. The total number of patients to include is 150. The sample size calculations were carried out using R software version 3.1.0 (library MKmisc, function power.diagnostic.test) (25, 26, 27).

Statistical analysis

In this non-randomized study where each patient is his own control, the threshold $p<0.05$ will be taken into account to define the significance of the statistical tests. Analyses will be carried out in accordance with good statistical analysis practices after freezing of the database and will be carried out with the software R (version ≥ 3.1.0).

The normality of the dependent quantitative parameters will be determined by the Shapiro-Wilks test or by graphical verification of the symmetry of the distribution. When the normality of the distribution of such a parameter has been demonstrated, it will be described by its mean and its standard deviation. Otherwise it will be described by its median, the 25th and the 75th percentile. The qualitative parameters will be expressed in number and percentage.

For the main objective, the sensitivity of the ULD CT (compared to the LD CT) for the detection of nodules will be calculated and accompanied by a 95% confidence interval. For secondary objective 1, the number of TP, FP, TN, FN, PPV, NPV and Sp of the ULD CT (compared to LD CT) will be calculated. For secondary objectives 2, 5, 6 and 7, the concordance of the qualitative variables will be evaluated using the kappa coefficient. The concordance of the quantitative variables will be evaluated using Lin's concordance coefficient. For each coefficient, the 95% confidence interval will be given. For secondary objective 3, inter-observer reproducibility for qualitative variables will be evaluated using the kappa coefficient. It will be evaluated, for the quantitative variables, using the ICC (intra class coefficient). For each coefficient, the 95% confidence interval will be given. For

secondary objective 4, a logistic regression model will be implemented. The variable to be explained will be the result of detecting each nodule in ULD CT compared to the LD CT (0 = good detection / 1 = bad detection). The explanatory variables will be the age, sex and BMI of the patient, the location (lobe) and the size of the nodule. The size of the nodule can be used as a qualitative variable (<5mm, 5-10mm,> 10mm).

An interim analysis including the analysis of the primary endpoint will be performed after inclusion of the first 50 patients. This interim analysis will aim to: decide whether to continue or stop the study for futility and readjust the number of patients if necessary (if the characteristics of the patients included do not correspond to those initially planned (too many patients without nodules ≥4 mm)). In order to maintain an overall threshold of 5% in the final analysis, the interim analysis will be carried out with a threshold of 0.1% (28). The results of the interim analysis will be taken into account by the steering committee to propose modifications to the analysis plan. For this interim analysis, data from the confrontation between the two radiologists will be used.

Limitations

First limitation of our protocol is that we do not have a true screening population because there is no organized lung cancer screening program in our country yet. Therefore, our study population corresponds to patients routinely referred for lung nodule checkup or follow up instead of a risk-factor based population.

Another limitation is that ULD CT is easily recognizable as the image noise is increased as compared to LD CT, as well as ULD 50 and ULD 100 are possible to distinguish for an experienced radiologist. As a consequence, readers were not blinded for these, but for patient name, sex, age, clinical status, and CT report.

Recall bias is limited by a randomized order of presentation and cutting into several reading sessions.

Although we wanted to have a "western population", we decided not to include obese patients with a BMI>35, because ULD CT are of poorer quality, due to the need of more radiation-exposure to

produce acceptable images. Vardhanabhuti and al. recently found a loss of nodule detection with iterative reconstructed CT scanners at an effective dose of 0.14±0.01mSv for obese patients with BMI>38 (29).

We decided to test percentage of 50 and 100% of ASIR-V. Tang and al. tested ASIR-V from 10 to 100% in non-enhanced chest and showed ASIR-V has greater potential in reducing image noise and artifacts and maintaining image sharpness when compared to ASIR, and 60% ASIR-V had the highest image quality combining both the objective and subjective evaluation of images (30). This finding, although occurring after the design of our study is close to our chosen 50% level of ASIR-V.

Finally, our study has been conceived before the recommendations of the EU Position statement published at the end of 2017(31). Therefore, we measured manually the nodules instead of using computerized volumetry.

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AUTHOR CONTRIBUTIONS

M. Ludwig is the corresponding author and contributed to the conception of the study, to the inclusion of patients, to the blind reading of outcomes and to the drafting of the manuscript.

E. Chipon contributed to the conception of the study, to the drafting of the manuscript, and is responsible for data management and its integrity.

J. Cohen contributed to the conception of the study, to the inclusion of patients, to the blind reading of outcomes and to the revision of the manuscript.

E. Reymond contributed to the inclusion of patients, to the blind reading of outcomes and to the revision of the manuscript.

M. Medici contributed to the design and application of statistical analysis, and to the drafting of the manuscript.

A. Cole contributed to the blind reading of outcomes and to the revision of the manuscript.

A. Moreau Gaudry contributed to the conception of the study and to the revision of the manuscript.

G R Ferretti is the principal investigator of the study and contributed to the conception of the work, to the inclusion of patients, to the blind consensus of outcomes and to the revision of the manuscript.

All authors approved the final manuscript and agreed to be accountable for all aspects of the work.

COMPETING INTERESTS

The authors declare that they have no competing interests

CONSENT FOR PUBLICATION

Not applicable

ETHICS AND DISSEMINATION

This trial is registered on the ClinicalTrials.gov database (reference NCT03305978) (see supplementary file "trial registration data set"), and was approved by the relevant ethical committee (Comité de Protection des Personnes, CPP sud-est VI, France, 07/07/2017, CPP Reference: AU1342). The Protocol version is N°1.0- Date: May 4th 2017

All patients sign a consent form before being enrolled in the trial, in accordance with the Declaration of Helsinki II.

Once the statistical report is finalized, we plan to publish our results in an international scientific journal and present them in national and international congresses.

DATA STATEMENT

Legal restrictions (French personal data laws) prohibit the authors from making the minimal data set publicly available. These data are available upon request.

ACKNOWLEDGEMENTS

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REFERENCES

1. Globocan : Lung Cancer Estimated Incidence, Mortality and Prevalence Worldwide in 2012 http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx)
2. National Lung Screening Trial Research Team, Denise R. Aberle, Amanda M. Adams, Christine D. Berg, William C. Black, Jonathan D. Clapp, Richard M. Fagerstrom, et al. "Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening." *The New England Journal of Medicine* 365, no. 5 (August 4, 2011): 395–409. doi:10.1056/NEJMoa1102873
3. Yousaf-Khan U, van der Aalst C, de Jong PA, et al."Final screening round of the NELSON lung cancer screening trial: the effect of a 2.5-year screening interval." Thorax 2017;72:48-56. 10.1136/thoraxjnl-2016-208655
4. Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation and National Research Council. Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2.Washington, D.C: The National Academies Press; 2006

5. Kubo T, Ohno Y, Seo JB, Yamashiro T, Kalender WA, Lee CH, et al. "Securing safe and informative thoracic CT examinations-Progress of radiation dose reduction techniques". Eur J Radiol. 2017 Jan;86:313–9.

6. Kim, Yookyung, Yoon Kyung Kim, Bo Eun Lee, SeokJeong Lee, YonJuRyu, Jin Hwa Lee, and Jung Hyun Chang. "Ultra-Low-Dose CT of the Thorax Using Iterative Reconstruction: Evaluation of Image Quality and Radiation Dose Reduction." *AJR. American Journal of Roentgenology* 204, no. 6 (June 2015): 1197–1202. doi:10.2214/AJR.14.13629.

7. Vardhanabhuti, Varut, Robert J. Loader, Grant R. Mitchell, Richard D. Riordan, and Carl A. Roobottom. "Image Quality Assessment of Standard- and Low-Dose Chest CT Using Filtered Back Projection, Adaptive Statistical Iterative Reconstruction, and Novel Model-Based Iterative Reconstruction Algorithms." *AJR. American Journal of Roentgenology* 200, no. 3 (March 2013): 545–52. doi:10.2214/AJR.12.9424.

8. Ichikawa, Yasutaka, Kakuya Kitagawa, Naoki Nagasawa, Shuichi Murashima, and Hajime Sakuma. "CT of the Chest with Model-Based, Fully Iterative Reconstruction: Comparison with Adaptive Statistical Iterative Reconstruction." *BMC Medical Imaging* 13 (2013): 27. doi:10.1186/1471-2342-13-27.

9. Padole, Atul, Sarabjeet Singh, Jeanne B. Ackman, Carol Wu, Synho Do, Sarvenaz Pourjabbar, Ranish Deedar Ali Khawaja, et al. "Submillisievert Chest CT with Filtered Back Projection and Iterative Reconstruction Techniques." *AJR. American Journal of Roentgenology* 203, no. 4 (October 2014): 772–81. doi:10.2214/AJR.13.12312.

10. Montet, Xavier, Anne-Lise Hachulla, Angeliki Neroladaki, Frederic Lador, Thierry Rochat, Diomidis Botsikas, and Christoph D. Becker. "Image Quality of Low mA CT Pulmonary Angiography Reconstructed with Model Based Iterative Reconstruction versus Standard CT Pulmonary Angiography Reconstructed with Filtered Back Projection: An Equivalency Trial." *EuropeanRadiology* 25, no. 6 (June 2015): 1665–71. doi:10.1007/s00330-014-3563-5.

11. Yoon, Hyun Jung, Myung Jin Chung, Hye Sun Hwang, Jung Won Moon, and Kyung Soo Lee. "Adaptive Statistical Iterative Reconstruction-Applied Ultra-Low-Dose CT with Radiography-Comparable Radiation Dose: Usefulness for Lung Nodule Detection." *Korean Journal of Radiology* 16, no. 5 (October 2015): 1132–41. doi:10.3348/kjr.2015.16.5.1132

12. Sui, Xin, Felix G. Meinel, Wei Song, Xiaoli Xu, Zixing Wang, Yuyan Wang, Zhengyu Jin, Jiuhong Chen, Rozemarijn Vliegenthart, and U. Joseph Schoepf. "Detection and Size Measurements of Pulmonary Nodules in Ultra-Low-Dose CT with Iterative Reconstruction Compared to Low Dose CT." *European Journal of Radiology* 85, no. 3 (March 2016): 564–70. doi:10.1016/j.ejrad.2015.12.013

13. Nagatani Y, Takahashi M, Murata K, Ikeda M, Yamashiro T, Miyara T, Koyama H, Koyama M, Sato Y, Moriya H, et al "Lung nodule detection performance in five observers on computed tomography (CT) with adaptive iterative dose reduction using three-dimensional processing (AIDR 3D) in a Japanese multicenter study: Comparison between ultra-low-dose CT and low-dose CT by receiver-operating characteristic analysis".*Eur J Radiol. 2015 Jul; 84(7):1401-12. Epub 2015 Apr 2*

14. Huber, Adrian, Julia Landau, Lukas Ebner, Yanik Bütikofer, Lars Leidolt, Barbara Brela, Michelle May, Johannes Heverhagen, and Andreas Christe. "Performance of Ultralow-Dose CT with Iterative Reconstruction in Lung Cancer Screening: Limiting Radiation Exposure to the Equivalent of Conventional Chest X-Ray Imaging." *EuropeanRadiology*, January 26, 2016. doi:10.1007/s00330-015-4192-3

15. Messerli M, Kluckert T, Knitel M, Wälti S, Desbiolles L, Rengier F, et al. "Ultralow dose CT for pulmonary nodule detection with chest x-ray equivalent dose - a prospective intra-individual comparative study". EurRadiol. 2017 Aug;27(8):3290–9.

16. Neroladaki, Angeliki, Diomidis Botsikas, Sana Boudabbous, Christoph D. Becker, and Xavier Montet. "Computed Tomography of the Chest with Model-Based Iterative Reconstruction

Using a Radiation Exposure Similar to Chest X-Ray Examination: Preliminary Observations." *EuropeanRadiology* 23, no. 2 (February 2013): 360–66. doi:10.1007/s00330-012-2627-7.

17. De Marco P, Origgi D. "New adaptive statistical iterative reconstruction ASiR-V: Assessment of noise performance in comparison to ASiR". J Appl Clin Med Phys. 2018 Mar;19(2):275-286. doi: 10.1002/acm2.12253. Epub 2018 Jan 24. PubMed PMID: 29363260; PubMed Central PMCID: PMC5849834
18. Gierada DS, Pinsky P, Nath H, Chiles C, Duan F, Aberle DR. "Projected outcomes using different nodule sizes to define a positive CT lung cancer screening examination". J Natl Cancer Inst. 2014;106:dju284
19. Bankier A, MacMahon H, Goo JM, et al. Recommendations for Measuring Pulmonary Nodules at CT: A Statement from the Fleischner Society. Radiology 2017;285:584-600 doi:10.1148/radiol.2017162894
20. Ahn MI, Gleeson TG, Chan IH et-al. "Perifissural nodules seen at CT screening for lung cancer". Radiology. 2010;254 (3): 949-56. doi:10.1148/radiol.09090031
21. Task Group on Control of Radiation Dose in Computed Tomography. "Managing Patient Dose in Computed Tomography. A Report of the International Commission on Radiological Protection." *Annals of the ICRP* 30, no. 4 (2000): 7–45
22. Exposition de la population française aux rayonnements ionisants liée aux actes de diagnostic médical en 2012. Rapport IRSN PRP-HOM N°2014-6
23. Jankowski, A., T. Martinelli, J. F. Timsit, C. Brambilla, F. Thony, M. Coulomb, and G. Ferretti. "Pulmonary Nodule Detection on MDCT Images: Evaluation of Diagnostic Performance Using Thin Axial Images, Maximum Intensity Projections, and Computer-Assisted Detection." European Radiology 17, no. 12 (December 2007): 3148–56. doi:10.1007/s00330-007-0727-6.

24. Revel MP, Bissery A, Bienvenu M, Aycard L, Lefort C, Frija G. Are two-dimensional CT measurements of small noncalcified pulmonary nodules reliable? Radiology. 2004 May;231(2):453-8. PubMed PMID: 15128990.

25. A. Flahault, M. Cadilhac, and G. Thomas (2005). Sample size calculation should be performed for design accuracy in diagnostic test studies. Journal of ClinicalEpidemiology, 58(8):859-862.

26. H. Chu and S.R. Cole (2007). Sample size calculation using exact methods in diagnostic test studies. Journal of ClinicalEpidemiology, 60(11):1201-1202.

27. M.R. Chernickamd C.Y. Liu (2002). The saw-toothed behavior of power versus sample size and software solutions: single binomial proportion using exact methods. Am Stat, 56:149-155.

28. Kenneth F Schulz, David A Grimes. Multiplicity in randomised trials II: subgroup and interim analyses. Lancet 2005; 365: 1657–61

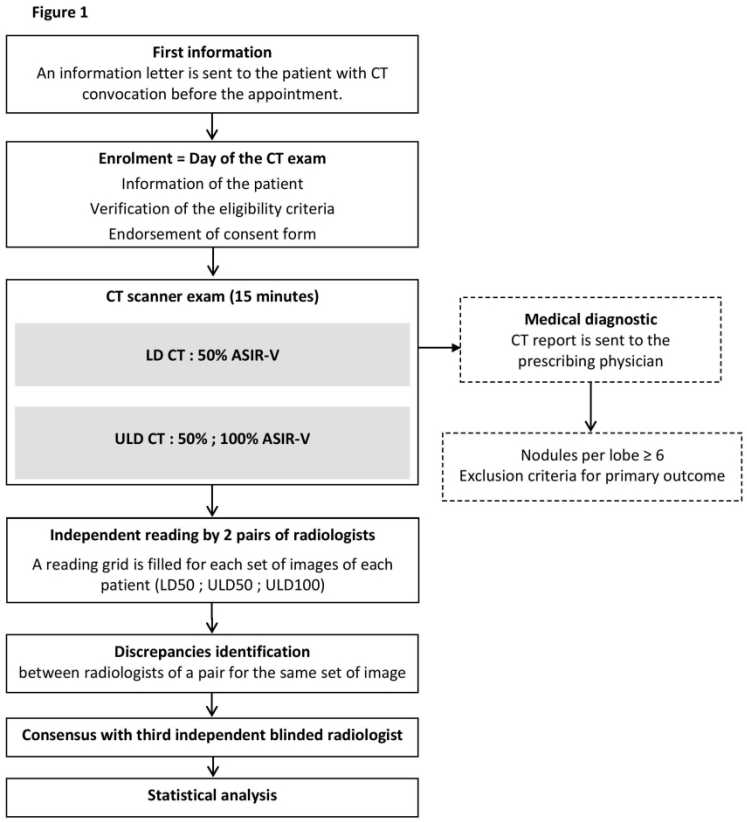
29. Vardhanabhuti V, Pang CL, Tenant S, Taylor J, Hyde C, Roobottom C. "Prospective intra-individual comparison of standard dose versus reduced-dose thoracic CT using hybrid and pure iterative reconstruction in a follow-up cohort of pulmonary nodules-Effect of detectability of pulmonary nodules with lowering dose based on nodule size, type and body mass index". Eur J Radiol. 2017 Jun;91:130-141. doi: 10.1016/j.ejrad.2017.04.006

30. Tang H, Yu N, Jia Y, Yu Y, Duan H, Han D, et al. "Assessment of noise reduction potential and image quality improvement of a new generation adaptive statistical iterative reconstruction (ASIR-V) in chest CT". Br J Radiol. 2018 Jan;91(1081):20170521

31. Oudkerk M, Devaraj A, Vliegenthart R, et al. European position statement on lung cancer screening. Lancet Oncol 2017;18: e754–66. http://dx.doi.org/10.1016/S1470-2045(17)30861-6

FIGURE 1 legend:

Study Flow chart. ASIR-V ®, adaptive statistical iterative reconstruction-Véo (GE medical Healthcare, Milwaukee, WI, USA); CT, computed tomography; LD, low dose; LD50, low dose CT with 50% ASIR-V reconstruction; ULD, ultra-low dose; ULD50, ultra-low dose CT with 50% ASIR-V reconstruction, ULD 100, ultra-low dose CT with 100% ASIR-V reconstruction



Study Flow chart. ASIR-V ®, adaptive statistical iterative reconstruction-Véo (GE medical Healthcare, Milwaukee, WI, USA); CT, computed tomography; LD, low dose; LD50, low dose CT with 50% ASIR-V reconstruction; ULD, ultra-low dose; ULD50, ultra-low dose CT with 50% ASIR-V reconstruction, ULD 100, ultra-low dose CT with 100% ASIR-V reconstruction.

210x297mm (300 x 300 DPI)

Trial registration data set :

Primary registry and trial identifying number	ClinicalTrials.gov NCT03305978
Date of registration in primary registry	September 26, 2017
Secondary identifying numbers	38RC17.132
Source(s) of monetary or material support	University Hospital, Grenoble
Primary sponsor	University Hospital, Grenoble
Secondary sponsor(s)	French Thoracic Imaging Society
Contact for public queries	Emilie CHIPON, PhD, +33476767313, echipon@chu-grenoble.fr
Contact for scientific queries	Gilbert FERRETTI, MD PhD, +3376767313, gferretti@chu-grenoble.fr
Public title	Pulmonary Nodule Detection: Comparison of an Ultra Low Dose vs Standard Scan.
Scientific title	Detection of Pulmonary Nodules: Comparison of Ultra-low-dose Chest CT (Approaching a Two Views Chest X-ray Radiation) and Standard Low Dose CT. A Monocentric, Prospective, Non-randomized, Comparative, Open-label Study With Blind Reading of the Judgment Criteria
Country of recruitment	France
Health condition(s) or problem(s) studied	Lung cancer screening, radiation exposure
Intervention(s)	Device: Ultra low dose chest CT An additional ultra low dose CT row is performed for every subject besides standard diagnostic low dose chest CT. Other Name: Revolution CT (GE Healthcare) 442507CN0, equiped with ASIR V
	Device: Low dose chest CT standard diagnostic low dose chest CT Other Name: Revolution CT (GE Healthcare)
Key inclusion and exclusion criteria	Ages eligible for study: ≥18 years Sexes eligible for study: both Accepts healthy volunteers: no
	Inclusion criteria : Patients referred for non enhanced chest CT for following indications : - lung nodule search or control - nodular abnormality on chest X ray - statement of COPD or emphysema - asbestos exposure - nodule localization before radio frequency ablation - assessment of disease extent of an extra thoracic cancer (in case of iodinated intravenous contrast agent contraindication) - statement before extrathoracic transplantation (in case of iodinated intravenous contrast agent contraindication) Affiliated with the french social security Who signed consent
	Exclusion criteria : Inability to lie down and stay still during the examination Inability to hold breath more than 5 seconds Pneumonia in the last 3 months Body mass index more than 35kg/m² exclusion period of another interventionnal study

	referred for articles L1121-5 to L1121-8 of french public health code Pregnant or breastfeeding women
Study type	Interventional
	Allocation: Non-Randomized Intervention Model: Sequential Assignment Intervention Model Description: Major Patient Addressed for Thoracic CT without Injection of Contrast Masking: Single (Outcomes Assessor) Masking Description: blinding evaluation of criteria
	Primary purpose: diagnostic
Date of first enrolment	October 3, 2017
Target sample size	150
Recruitment status	Recruiting
Primary outcome(s)	Ultra low dose CT lung nodule detection sensibility [Time Frame: 22 months] Detection rate (%) of ≥4mm lung nodules in ultra low dose chest CT versus standard low
Key secondary outcomes	- Ultra low dose CT diagnostic performances of lung nodule detection [Time Frame: 22 months] :true positives, false positives, true negatives, false negatives, positive predictive value, negative predictive value, specificity, of ≥4mm lung nodules detection within ultra low dose chest CT versus standard low dose chest CT - Concordance of ≥4mm lung nodules characteristics between ultra low dose and standard low dose chest CT [Time Frame: 22 months] : comparison of size, density, type (true nodule or intrapulmonary ganglion) of ≥4mm lung nodule between ultra low dose and standard low dose chest CT - Ultra low dose CT inter-observer reproducibility [Time Frame: 22 months] : inter observer reproducibility for size, density and type of ≥4mm lung nodule detected in ultra low dose CT - Influence of subjects characteristics, nodule location, and nodule size on detection between ultra low dose and standard low dose chest CT [Time Frame: 22 months] : analysis of subjects characteristics (age, gender, body mass index), ≥4mm nodule location, and ≥4 mm nodule size on detection between ultra low dose and standard low dose chest CT - Concordance of emphysema characteristics between ultra low dose and standard low dose chest CT [Time Frame: 22 months] : comparison of emphysema detection, type (centrilobular, paraseptal, panlobular, bullous) and distribution between ultra low dose and standard low dose chest CT - Concordance of coronary calcification detection and quantification between ultra low dose and standard low dose chest CT [Time Frame: 22 months] : Comparison of Weston scores between ultra low dose and standard low dose chest CT - Concordance of bronchial abnormalities evaluation between ultra low dose and standard low dose chest CT [Time Frame: 22 months] : comparison of detection of bronchial thickening or dilatation between ultra low dose and standard low dose chest CT
Ethics Review	approved by the relevant ethical committee (Comité de Protection des Personnes, CPP Sud-Est VI, France, CPP Reference: AU1342), on July 7, 2017

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	17
Protocol version	#3	Date and version identifier	18
Funding	#4	Sources and types of financial, material, and other support	16
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1;16
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	2

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6
Objectives	#7	Specific objectives or hypotheses	7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	11
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n/a
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	n/a

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	n/a
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	16
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	n/a
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Data access	#29	Statement of who will have access to the final trial dataset,	19

		and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a