Study Protocol

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HANSE - **H**olistic implementation study **A**ssessing a **N**orthern German interdisciplinary lung cancer **S**creening **E**ffort

Population-based Screening Study -Prospective, randomized comparator controlled

HANSE STUDIE

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ARCN	Airway Research Center North
ADR	Adverse drug reaction
AE	Adverse event
AI	Artificial Intelligence
BMI	Body mass index
BREATH	Biomedical Research in End-stage and Obstructive Lung Disease Hannover
CAD	computer-assisted detection/ computer-aided diagnosis
CHERH	Center for Health Economics Research Hannover
CT	Computed tomography
DSGVO	Datenschutz-Grundverordnung
DRG	Deutsche Röntgengesellschaft
ECG	electrocardiogram
eCRF	Electronic case report form
gGmbH	gemeinnützige Gesellschaft mit beschränkter Haftung
IEC	Independent Ethics Committee
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
LDCT	Low-dose computed tomography
LungRADS	Lung CT Screening Reporting & Data System
MDT	Multidisciplinary tumor board
PanCan	Pan-Canadian Early Detection of Lung Cancer
PLCO	Prostate, lung, colorectal, and ovarian cancer screening
SAE	Serious adverse events
VDT	Volume doubling time

RESPONSIBLE PARTIES

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PROTOCOL SYNOPSIS

APPLICANT/ COORDINATING INVESTIGATOR	Prof. Dr. Jens Vogel-Claussen (Principal Investigator) Dr. Sabine Bohnet Prof. Dr. Martin Reck
TITLE OF STUDY	HANSE - **H**olistic implementation study **A**ssessing a **N**orthern German interdisciplinary lung cancer **S**creening **E**ffort
BACKGROUND /RATIONALE:	Germany has a long history of offering screening programs for cancers, such as breast, colorectal, and, more recently, cervical and skin cancer. Screening for lung cancer, however, which causes more deaths than any other cancer in men and is the second leading cancer death in women (not far behind breast cancer), has not been implemented to date. Only very recently, IQWiG in a preliminary assessment of low-dose CT screening, concluded that the benefits from screening outweigh potential risks. However, an implementation of a national lung cancer screening program, which would be covered by the general health insurance, will likely not be implemented before 2022. Nonetheless, the IQWiG report also comments on important criteria for implementing lung cancer screening in Germany using low-dose CT: 1. It would be necessary to determine criteria that define a high-risk population. Various risk forecasting models are currently being propagated to enable a more precise selection of high-risk individuals. Their reliability and repeatability needs to be checked. 2. Integration of access to a smoking cessation program. 3. Quality assurance measures must be taken into account, including standardized protocols for the evaluation of the CT images and the subsequent follow-up checks as well as the invasive diagnostic tissue sampling procedures. The HANSE study is primarily intended as a pilot to provide evidence that a holistic and effective lung cancer screening program can be implemented in Germany and that such a screening program can be integrated in the current infrastructure of certified lung cancer centers.
OBJECTIVE(S)	**Primary Objectives:** The primary goal of this study is to compare the efficiency of the $PLCO_{M2012}$ >1.58% (6 year risk) risk score and the NELSON inclusion criteria in identifying patients with lung cancer in the age group 55-79 years. To that end, the $PLCO_{M2012}$ model and the NELSON inclusion criteria will be compared (i) primarily regarding the positive predictive value of the two inclusion methods for lung cancers detected after 2 screening rounds in the study population and **Secondary Objectives:** (ii) secondarily regarding the following hierarchically ordered key-secondary endpoints: 1. Proportion of individuals selected for screening

	2. Proportion of lung cancers detected after 5 years 3. Proportion of lung cancers detected after 5 years in the high-risk population 4. Sensitivity of the two inclusion methods in lung cancer detection after 5 years 5. Specificity of the two inclusion methods in lung cancer detection after 5 years The main secondary objective of this trial is to document that: 1. Reporting of the coronary artery calcium score from low dose computed tomography (LDCT) data will lead to an increase in the rate of preventive cardiovascular treatments and reduced cardiovascular mortality. Additional objectives are to show that: 1. Effective smoking cessation counselling is implemented as part of the screening program (urine cotinine check in quitters). 2. CT derived information on tobacco related lung destruction, such as emphysema, may influence the smoking cessation rate. 3. Structured reporting of clinically relevant non-cardiac incidental findings, e.g., emphysema or lung fibrosis, will lead to early detection and improved management of diseases. 4. Adding the PanCan algorithm to the LungRads1.1 algorithm for nodule management increases the efficiency. 5. Assessment of various blood-based or exhalation-based biomarkers may provide additional translational information in positive LDCT cases with subsequent biopsy, which may have an impact on the effectiveness of the LDCT test. 6. Cost effectiveness analysis on recruiting strategies, risk models used, effectiveness on smoking cessation and cardiovascular mortality is implemented.
INTERVENTION(S)	Experimental intervention: Low-dose computed tomography with lung nodule evaluation (LungRADS1.1, high-risk score group), randomized reporting of coronary artery calcium score, %emphysema Control intervention: No CT (low risk score group) No coronary artery calcium score and no % emphysema report, Follow-up per patient: 1 year (10 years, follow-up study) Duration of intervention per patient: 1 year (10 years, follow-up study)
KEY INCLUSION AND EXCLUSION CRITERIA	Key inclusion criteria: 1. Male and female subjects aged 55-79 years 2. Current or former smokers 3. Subjects with calculated risk score $PLCO_{M2012}$ ≥1.58% (6 yrs.) or NELSON inclusion criteria (current or former smokers [those who had quit ≤10 years ago] who had smoked >15 cigarettes a day for >25 years or >10 cigarettes a day for >30 years). 4. Able and willing to give written informed consent In addition, non-qualifying subjects fulfilling inclusion criteria 1 (age), 2 (smoking history) and 4 (consent), but do not meet the inclusion criterion 3 (risk too low) will be asked to volunteer by contributing long-term outcome data informing of the

	development of lung cancer or death from lung cancer (about n=7100 randomly selected from all 3 centers, low-risk group). These subjects will be contacted via mail after a minimum of 5 year follow up to inquire if they developed lung cancer in the time between their recruitment and present. Non-responders will be followed by local registries and by phone. New lung cancer cases will be verified using official hospital or cancer registry documents. Key exclusion criteria: 1. Comorbidity, which would unequivocally contraindicate either screening or treatment if lung cancer is detected. 2. History of chest CT within the past year preceding the invitation. 3. Inability to undergo non-contrast CT (e.g. ≥ 200 kg body weight, inability to lie flat). 4. Pregnancy 5. Risk of non-compliance with study procedures. - Unable to give written consent - Patient`s inability to fill in the questionnaire self-dependent - Limited knowledge of the German language - Inability to travel, residents of care facilities, etc.
OUTCOME(S)	Primary endpoint: Positive predictive value (PPV) for lung cancer detection with different inclusion methods (NELSON vs. PLCO) after 2 screening rounds. Secondary endpoints: Key secondary endpoint(s): 1. Proportion of individuals selected for screening within the high-risk population 2. Proportion of lung cancers detected with different inclusion methods (NELSON vs. PLCO) within the overall study population after 5 years 3. Proportion of lung cancers detected with in the high-risk population after 5 years 4. Specificity within the overall population after 5-year follow-up 5. Sensitivity within the overall population after 5-year follow-up Secondary endpoints: 1. **Rate of initiation of cardiovascular treatments** (in particular lipid-lowering) in the calcium score reporting group vs. the non-reporting group after year 1 of study. 2. **Efficiency of nodule management algorithms** (LungRads1.1 + PanCan) will be evaluated according to - The number of patients sorted in the category (a) “Next surveillance scan” AND - The number of patients with lung cancer sorted into category (b) “early recall scan”, or (c) “diagnostic evaluation”. 3. **Success of screening program.** Based on all individuals enrolled. Definition of success is calculated using:

	a. Response rate (1. Respondents to questionnaire / invitation: those who send their smoking history & other relevant data; 2. among the above respondents, those who are eligible by one of the two criteria, or both; 3. those who are eligible, and actually take part in the screening), number of drop-outs, effectiveness of patient recruitment via mailings vs. GPs referrals (individual response rates) b. Reliability of PLCO risk scoring (self-reported vs. on site assessment) c. Percentage of subjects receiving an adequate low-dose CT scan and report according to DRG guidelines (number of diagnostic CTs/number of all CTs) d. Percentage of subjects receiving adequate follow-up procedures 5. **Quality of screening program** a. CT reading performance (2nd reader vs. CAD vs. AI) b. Quality of lung nodule management c. Frequency of detection and management of incidental findings from low dose chest CT (emphysema, coronary heart disease, etc.) d. LDCT dose management 6. **Smoking cessation** a. Success of smoking cessation counseling based on number of participants quitting with or without revealing additional health risks (emphysema score, coronary calcium score or both). 7. **Blood-based and exhalation- based biomarkers** a. Evaluation of various blood-based or exhalation- based biomarkers in positive LDCT cases with subsequent biopsy on the positive predictive value of the LDCT test. 8. **Cost-effectiveness analysis** a. Main objectives of the modelling study are to investigate the impact of different components of LDCT lung cancer screening on the long-term all-cause mortality and cost-effectiveness. Key components include risk score-based selection criteria, nodule management protocols, threshold values of imaging biomarkers for cardio-vascular diseases and COPD, and inclusion of smoking cessation programs. (performed by Center for Health Economics Research Hannover (CHERH) b. Comparison of patient recruitment strategies: Cost-effectiveness of register-based mailing campaign vs. GP referrals in terms of recruitment of qualified screening subjects (CHERH).
STUDY TYPE	Population-based Screening Study - Prospective, randomized comparator controlled
STATISTICAL ANALYSIS	**Primary analysis** The primary and key-secondary endpoints of this study will be calculated from the following two fourfold tables summarizing the distribution of included patients and patients with detected lung cancer:

Table 1

Number of Participants by Screening Eligibility			
		NELSON	
		+	-
$PLCO_{m2012}$	+	A	B
	-	C	D*

Table 2

Number of detected lung cancers by Screening Eligibility			
		NELSON	
		+	-
$PLCO_{m2012}$	+	a	b
	-	c	d*

Please note that * indicates volunteers with a low risk score, which are both PLCO and NELSON negative at inclusion.

PPV NELSON = (a+c) / (A+C); PPV PLCO = (a+b) / (A+B). For testing the null-hypothesis of equal PPVs for lung cancer detected in PLCOm2012-selected versus NELSON-selected individuals the weighted generalized score statistic developed by Kosinski will be used (20).

Secondarily, the proportion of lung cancers detected will be calculated as prop_lung(PLCO) = (a+b) / (a+b+c+d*) and prop_lung(NELSON) = (a+c) / (a+b+c+d*) after a follow up period of 5 years.

The proportion of individuals selected for screening will be calculated as prop_screening(PLCO) = (A+B) / (A+B+C) and prop_screening(NELSON) = (A+C) / (A+B+C).

Additionally, also the proportion of lung cancers detected in the identified high-risk population (PLCO or NELSON positive) will be calculated, using (a+b+c) as denominator and the proportion of individuals selected for screening within the low-risk population will also be calculated using (A+B+C+D*) as a denominator.

Specificities of the risk scores will be calculated after 5 years as spec(PLCO)=(C+D* – c-d)/(A+B+C+D* – a –b-c-d*) and spec(NELSON)=(B+D* – b-d)/(A+B+C+D* – a –b-c-d*).

The primary and key-secondary endpoints will be compared between PLCO and NELSON in a hierarchical at a two-sided type-I-error of 5% to control the overall type-I-error at 5% (according to the hierarchy of endpoints outlined above). For testing the null-hypothesis of no difference between the risk scores regarding the proportion of lung cancers detected, McNemar's Test will be used.

Description of the primary analysis and population:
The primary analysis will be conducted of all volunteers within the overall study population including the low-risk population and the high-risk population.

(i) **Power calculation for the primary endpoint**

Sample size calculation is based on data from the German Health Update study (GEDA; "Gesundheit in Deutschland aktuell") - a health monitoring program consisting of cross-sectional surveys conducted by the Robert Koch Institute to provide data on health and disease, health determinants and health behaviors from nationally representative samples of adults in Germany (20). Between 2008 and 2013, three GEDA studies were carried out, in 2008–2009, 2009–2010 and 2012–2013, involving a total of 62,606 computer assisted telephone interviews (23, 24). Based on this dataset the PLCO risk score was adjusted to a level (5-year risk of 1.314%, or 6-year risk of 1.58% [rounded]) were the NELSON inclusion criteria and the PCLO risk score are equally weighted in the German population aged 55-79 to include the same amount of volunteers in each group (table 3)

Table 3:

Risk threshold of 0.01314 (5y risk,weighted, scaled to 5000 participants) - Eversmokers aged 55-79				
		Nelson		
		0	1	
PLCO	0	7095.8 (21.8)	1070.25 (9.8)	
	1	1072.73 (27.0)	2857.04 (112.2)	

Number of ever smokers (predicted cancers) GEDA dataset (23, 24).
Between parentheses are the 5-year case numbers predicted by the PLCO model.

In a study by Hüsing & Kaaks (24) this model was found to accurately predict absolute lung cancer incidence compared to incidence actually observed (cancer registry data).

However, for power calculations one cannot directly assume that predicted 5-year incidence corresponds to the number of LC cases that will be detected by two CT screenings over a 1-year interval.

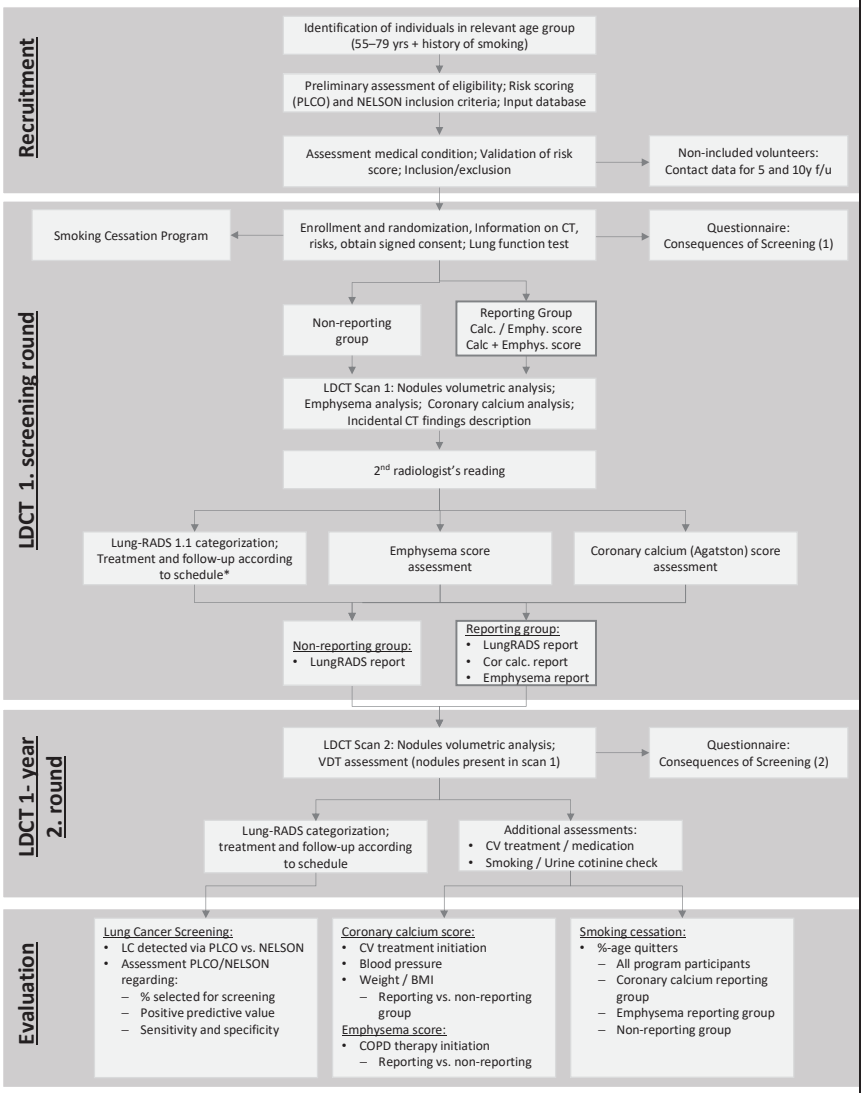
To estimate the number of expected CT-detected cases (two screens, 1-year interval) we extrapolated from observations in the LUSI trial. LUSI included participants 50-69 years of age who met the smoking criteria of NELSON. In a total of 2029 participants in the screening arm, 34 LC cases were detected in the first two screening rounds (22 at prevalence screen, and 12 at the first incidence screen).

From GEDA data, using the PLCO model, we estimated that, compared to individuals who meet the inclusion criteria of LUSI (age 50-69, and smoking criteria identical as in NELSON) the (5-year) LC incidence is 1.72 times higher for individuals in the higher age range (55-79, + NELSON smoking criteria) chosen for the present study.

	For the present study, we thus estimated an expected overall number of CT-detected cases of 144:34 x 5000/2029 x 1.72 = 144 We assume that these 144 CT-detected cases will be proportionally distributed as those in Table 3 (i.e., as with predicted 5-year incidence without screening). The numbers in Table 3 suggest that the PPV of the PLCO (risk-based, with 6-year risk threshold of 1.58%) will be 14% higher than the PPV of NELSON. For comparing positive predictive values from a paired diagnostic study, the weighted generalized score statistic proposed by Kosinski (20) will be used to test the Null-hypothesis of the PPVs being equal for Nelson and PLCO. Using a two-sided type-I error rate of 5%, the power of the primary comparison was estimated with a simulation study based on the above described proportions. Assuming an overall number of 5000 patients who are selected by the Nelson or the PCLO criterion, and number of patients which are positive by Nelson or PLCO only are simulated as a realization of a multivariate variable with n=5000 and proportions (2857/5000, 1070/5000 and 1072/5000 respectively) as n_both, n_Nelson and n_PLCO. Subsequently, the number of cancers detected was calculated from independent Binominal variables for each of the following conditions. Number of cancers in the group of patients who are Nelson and PLCO positive: Bin(n_both, (144/149)*(112/2857)) Number of cancers in the group of patients who are Nelson positive and PLCO negative: Bin(n_Nelson, (144/149)* (10/1070)) Number of cancers in the group of patients who are Nelson negative and PLCO positive: Bin(n_PLCO, (144/149)* (27/1072)) The empirical power was estimated as the proportion of 10,000 simulation runs, where the weighted generalized score statistic (20) applied to the simulated data showed a p-value smaller than 5%. Based on the above procedure, the estimated power to reject the null-hypothesis of equal PPVs between the NELSON and the PLCO score is 80,3%. For the HANSE study the calibrated threshold for the PLCO 5 year risk score of 1,314% was converted to a 6year threshold of 1,58% , because the original PLCO risk score calculates the 6year risk and thus the original calculators by Tammemägi et al. can be used for the HANSE study (13). For this conversion linearity between year 5 and 6 was assumed. (ii) Sample size for the evaluation of **initiation of cardiovascular therapy** within 1 year after randomization has been calculated using Chi-Square Test and two-sided type-I-error rate of 5% based on the results of the ITALUNG study (15,16), where for 44% of all patients coronary artery calcification (CAC) was detected. In the ITALUNG study, 63% of patients with CAC were on cardiovascular treatment without receiving results of their low dose CT screening. For this study, where the patients are randomized to either reporting or non-reporting of CT screening results, we conservatively assume that the non-reporting group shows a rate of cardiovascular treatment of 68%. In contrast, as an effect of reporting the screening results, we assume that in the reporting group 73% of patients receive cardiovascular treatment, so the effect of reporting the CT results is assumed to be an increase of 5 percentage

	points in the cardiovascular treatment rate. Acknowledging that only 44% of all patients are assumed to show CAC on low dose CT, the expected difference between the reporting and non-reporting group is (73%-68%) * 44% = 2.2%. Equivalently, the assumed rate ratio between the reporting and non-reporting group is (73% * 44*) / (68% *44%) = 1.07. With 2500 patients randomized to each arm and using a Chi-Square Test with a two-sided type-I-error rate of 5% for testing the null-hypothesis of no difference between the groups, the statistical power is 97%. (iii) To evaluate the power of potential **longitudinal follow-up** studies based on this screening trial, the power for the 10 year mortality endpoint has been calculated based on the results of the NELSON study using a Chi-Square Test with a two-sided type-I-error rate of 5% for testing the null-hypothesis of no difference in 10-year mortality rates between the reporting and non-reporting groups. In line with the results of the NELSON study, we assume a 10 year cardiovascular mortality rate in the non-reporting group of 2.7%. Assuming a rate ratio of 0.6 between the reporting and non-reporting group (or equivalently, a 10-year mortality rate of 1.6%), the difference between the reporting and non-reporting group can be shown with a power of 75%. In order to include 5000 volunteers in the high-risk group in the HANSE study 5500 need to be recruited to account for drop outs (10%). **Conclusion: With an overall sample size of 5,000 subjects (and 2500 volunteers randomized to the reporting and non-reporting group) the study is well-powered to investigate the primary hypothesis, evaluate potential cardiovascular benefit and provide the basis to investigate mortality in a follow-up study.**
SAMPLE SIZE	To be assessed for eligibility: **n = 350 000** To be allocated to trial: **n = 5500 + all recruited volunteers with low risk scores/low NELSON criteria (low risk group)** To be analysed: **n = 5000 + 7100 low risk group**
TRIAL DURATION	First patient in to last patient out (months): 30 Duration of the entire trial (months): 36 (longitudinal extension up to 10 years) Recruitment period (months): 12
PARTICIPATING CENTERS	**n = 3** Hannover Medical School (BREATH) Universitätsklinikum Schleswig-Holstein - Campus Lübeck (ARCN) LungenClinic Grosshansdorf gGmbH (ARCN) In the 1st and 2nd screening round CT imaging will be performed in a mobile CT scanner in a truck serving all 3 sites.
RELEVANCE TO DZL	With this flagship trial, the DZL is a key driver for implementation of a structured and cost-effective lung cancer screening program in northern Germany defining the high-risk population and including comorbidity assessment, a biomarker program and smoking cessation.

STUDY FLOW CHART



* **Follow-up schedule**

LungRADS Categories:

- 1, 2: 1 year LDCT
- 3: 6 months LDCT; VDT assessment
- 4a: 3 months LDCT; VDT assessment
- 4b, X: MDT, tissue sampling depending on the probability of malignancy and comorbidities.

AMENDMENT HISTORY

Date	Brief description of change	Administrative Change / Amendment / New Protocol Version.
15.09.2020	N/A	Initial Protocol Version 1.0
23.11.2020	Adjustment of study objectives after epidemiological review and related power calculation of primary endpoint	Amendment Protocol Version 2.0
09.02.2021	Administrative changes only: Additional clarifications for recruitment methods, potential sampling bias and biomarkers	Amendment Protocol Version 2.1

MILESTONES

Date	Milestone
August 2020	Final study protocol
August 2020	Contract Astra Zeneca
August 2020	Contract CRO
August 2020	Contract Coreline
August 2020	Contract truck/CT
September 2020	Ethics approval
September 2020	BfS application
March 2021	Study fully set-up
April 2021	Start of enrollment: First patient in
August 2023	Date of last data entry in database
September 2023	Date of Database Lock (Clean Database)
December 2023	Publication and Final report

1. BACKGROUND AND RATIONALE

1.1 Background

Lung cancer caused more than 45,000 deaths in Germany in 2016, with 57,000 newly diagnosed cases. The death toll from lung cancer corresponds to 19.9% of deaths from all cancer combined, whereas the incidence of lung cancer is only 11.5% of all cancer cases (1). Smoking (or a history of smoking) is the main risk factor, accounting for approx. 9/10 cases in men and 6/10 cases in women. Although tobacco usage has declined in recent years in Germany, rates are still higher than in many other European countries (2).

Consequently, lung cancer will continue to be one of the most important health issues in Germany with a massive impact on the health system in the years to come. When compared to other cancers, lung cancer has a particularly poor prognosis. Approx. 70% of patients are diagnosed at late stages - stage III or IV of the disease, when their 5-year survival is 16% and 4% (3).

At earlier stages, lung cancer is more amenable for curative treatment, thus prompting efforts to identify cancer at early stages by screening programs. However, initial screening trials using chest radiography have not led to a reduction in lung cancer mortality.

More recently, a US landmark study (NLST) has shown that low-dose CT (LDCT) of the chest detected more nodules and cancers, including early-stage cancers than chest radiography, and, in particular, reduced mortality from lung cancer among the high-risk population (4).

Since the first landmark study, however, several smaller European trials have provided inconclusive results in evidence that LDCT will lead to a reduced cancer or all-cause mortality (5, 6). Only recently, the LUSI study (5), and, in particular, the NELSON trial with more than 15,000 participants (6) have shown convincingly that low-dose computed tomography (LDCT) screening may reduce lung-cancer mortality in a high-risk population.

However, despite the high prevalence and associated high mortality, a national screening program for lung cancer has not been implemented in Germany.

1.2 Rationale

Germany has a long history of offering screening programs for cancers, such as breast, colorectal, and, more recently, cervical and skin cancer. Screening for lung cancer, however, which causes more deaths than any other cancer in men and is the second leading cancer death in women (not far behind breast cancer), has not been implemented to date.

Only very recently, IQWiG in a preliminary assessment of low-dose CT screening, concluded that the benefits from screening outweigh potential risks (7). However, an implementation of a national lung cancer screening program, which would be covered by the general health insurance, will likely not be implemented before 2022. Nonetheless, the IQWiG report also comments on important criteria for implementing lung cancer screening in Germany using low-dose CT:

1. It would be necessary to determine criteria that define a high-risk population. Various risk forecasting models are currently being propagated to enable a more precise selection of high-risk individuals. Their reliability and repeatability needs to be checked.

2. Integration of access to a smoking cessation program.

3. Quality assurance measures must be taken into account, including standardized protocols for the evaluation of the CT images and the subsequent follow-up checks as well as the invasive diagnostic tissue sampling procedures.

The HANSE study is primarily intended as a pilot to provide evidence that a holistic and effective lung cancer screening program can be implemented in Germany and that such a screening program can be integrated in the current infrastructure of certified lung cancer centers.

The design of the HANSE study closely follows German and European recommendations for using risk scores to identify the population at greatest risk for lung cancer (8, 9, 10, 21). Moreover, HANSE will address one of the key questions concerning the most appropriate approach for recruiting and identifying the 'true' high-risk target population, which is crucial for the implementation of a cost-effective screening program (11, 12). To that end, HANSE is laid out specifically to address, whether NELSON inclusion criteria, or the $PLCO_{M2012}$ risk model will prove more reliable in selecting the true high-risk patients for the screening program in the age group 55-79y (13).

For the HANSE trial, 5,000 participants aged 55-79y who meet the NELSON and/or $PLCO_{M2012}$ 6 year risk >1.58% selection criteria will be included. Participants will undergo baseline and 1-year screening under defined conditions using low-dose computed tomography in three specialized lung cancer centers in northern Germany.

Standardized and quality-assured image analysis will be conducted using state-of-the-art artificial intelligence (AI)-based detection and nodule measurement software (AVIEW, Coreline Soft Company Ltd., South Korea) to support the radiologist. CT assessment of lung nodules will be done according to LungRADS 1.1 criteria, as well as volume doubling time according to the European position statement on lung cancer screening (14). Additionally, this trial integrates different recruiting strategies, a smoking cessation counselling program, includes a cost-effectiveness modelling, cardiovascular and lung comorbidity assessment, different lung nodule management strategies (Lung RADS 1.1. vs. PanCan vs. AI) and explores blood-based biomarkers in positive LDCT cases.

An additional objective of the HANSE study is to provide evidence for the potential of low dose CT in the diagnosis of diseases other than lung cancer, such as emphysema, but also cardio-vascular diseases, which to date has only been suggested by retrospective analyses of LDCT studies (15, 16). Low dose CT does allow to examine the coronary calcium score (Agatston score (17)), indicative of the coronary plaque status which has shown to correlate with the rate of future myocardial infarction, stroke and death due to cardiovascular disease (18). The trial will assess whether reporting of the score may have consequences in individuals with a positive

coronary calcium score seeking specialist consultation and initiating preventive cardio-vascular therapy.

The trial will further encompass a smoking cessation program and smoking cessation rate under the different experimental settings will be determined at 1-year follow-up. Specifically, the consequences on smoking status will be compared between the non-reporting group, the calcium score reporting group, the emphysema score reporting group vs. the non-reporting group in order to document a potential impact of reporting.

Additionally, this design feature allows to analyse long-term smoking cessation rates and mortality in a follow-up study at year 5 and 10 (not part of this funding period).

Besides that an extensive translational biomarker program with the assessment of potential predictive epigenetic signatures from blood samples and exhalation markers from exhalation samples in patients with positive findings on their LDCT scans will provide further insights about the potential predictivity of circulating and exhalatory markers for the early detection of lung cancer. In addition, blood samples will be collected optionally from the high-risk group at the 1st and 2nd screening round visit and stored in the DZL biobank for future research.

Furthermore, the Center for Health Economics Research Hannover (CHERH) develops a comprehensive microsimulation platform for the assessment of long-term performance and cost-effectiveness of nationwide lung cancer screening with LDCT based on the HANSE study data. Main objectives of the modelling study are to investigate the impact of different components of LDCT lung cancer screening on the log-term all-cause mortality and cost-effectiveness. Key components include risk score-based selection criteria, nodule management protocols, threshold values of imaging biomarkers for cardio-vascular diseases and COPD, and inclusion of smoking cessation programs.

In order to be successful with the aim to implement a holistic structured lung cancer screening program in northern Germany an interdisciplinary team of expert physicians from pneumology, radiology, cardiology, thoracic surgery, oncology, pathology and epidemiology works together in three certified lung cancer centers. To succeed with the aim of recruiting 5,000 high risk persons for LDCT screening within 12 months the interdisciplinary team works together with an experienced CRO and call center to create an efficient workflow and infrastructure using state of the art information technology. To achieve a structured cutting edge radiologist reading workflow for LDCT reporting, specialized LDCT screening software is used including AI based automated coronary artery calcium scoring and emphysema quantification in addition to the lung nodule management tools.

Taken together, HANSE is designed to address critical open issues concerning lung cancer screening programs, such as targeting and cost—effectiveness. In addition, inclusion of additional disease-related markers, such as the emphysema and coronary calcium scores will greatly enhance benefits of the screening program beyond lung cancer.

2. OBJECTIVES AND HYPOTHESES

2.1 Primary Objective(s) & Hypothesis(es)

Primary Objectives:

The primary goal of this study is to compare the efficiency of the $PLCO_{M2012}$ >1.58% (6 year risk) risk score and the NELSON inclusion criteria in identifying patients with lung cancer in the age group 55-79 years. To that end, the $PLCO_{M2012}$ model and the NELSON inclusion criteria will be compared

(i) primarily regarding the positive predictive value of lung cancers detected using the two inclusion methods.

2.2 Secondary Objective(s) & Hypothesis(es)

Key-Secondary Objectives:

The $PLCO_{M2012}$ model and the NELSON inclusion method will be compared

(ii) secondarily to the primary objective regarding the following hierarchically ordered key-secondary endpoints:

1. Proportion of individuals selected for screening
2. Proportion of lung cancers detected
3. Sensitivity and specificity of the scores in cancer detection

Secondary Objectives:

The main secondary objectives of this trial is to document that:

1. Reporting of the coronary artery calcium score from low dose computed tomography (LDCT) data will lead to an increase in the rate of preventive cardiovascular treatments and reduced cardiovascular mortality.

Additional objectives are to show that:

1. Effective smoking cessation counselling is implemented as part of the screening program (urine cotinine check in quitters).
2. CT derived information on tobacco related lung destruction, such as emphysema, may influence the smoking cessation rate.
3. Structured reporting of clinically relevant non-cardiac incidental findings, e.g., emphysema or lung fibrosis, will lead to early detection and improved management of diseases.
4. Adding the PanCan algorithm/AI to the LungRads1.1 algorithm for nodule management increases the efficiency.
5. Assessment of various blood-based or exhalation-based biomarkers may provide additional translational information in positive LDCT cases with subsequent biopsy, which may have an impact on the effectiveness of the LDCT test.
6. Cost effectiveness analysis on recruiting strategies, risk models used, effectiveness on smoking cessation and cardiovascular mortality is implemented.

3. METHODOLOGY

3.1 Study Design – General Aspects

The HANSE study is a prospective, randomized comparator controlled population-based screening study.

3.1.1 Data Source(s)

- Low-dose CT: Presence and grade of lung nodules according to LungRADS 1.1 criteria; Coronary calcium scores (Agatston score); Percent lung emphysema (Coreline Software), clinically relevant incidental findings.
- Patient questionnaire.
- Results of blood sample and exhalation sample analysis in LDCT positive patients.
- Lung function test (bodyplethysmography and diffusing capacity of the lungs for carbon monoxide)
- BMI, blood pressure
- Urine cotinine test
- healthcare costs for the HANSE study
- All data will be collected in the HANSE electronic case report form (eCRF)

3.2 Study Population

Male and female subjects age 55-79 years AND history of smoking. Population will be identified via local general population-based registries ("Einwohnermeldeämter") and informed about the screening study by mail. The registries are general population based local registries ("Einwohnermeldeamt"), where all inhabitants in a region are registered by law. We requested Name, birthdate and address from the 3 participating cites (Hannover, Lübeck and Hamburg) in the age group 55-79. Additional recruitment efforts via local physicians (GPs, specialists) and campaigns targeting the general public.

Mailed information package will contain a response element (paper) with questions concerning their smoking habits and history and link to study website. Interested individuals might either reply using the response element or input their data on the study website. Self-reported health data will be used to pre-qualify subjects based on PLCO / NELSON criteria.

Subjects with preliminary PLCO risk-score ≥1.58% (6 years) or NELSON inclusion criteria will be invited to one of the study centers (high-risk group). On site, all subjects will undergo validation of their risk scores, additional examination of their medical condition, medical history and current medication by qualified personnel. Data will be stored in specially designed database (Clinical Research Organisation – CRO).

Subjects, who did not meet the NELSON or PLCO criteria, will be asked to volunteer by contributing long-term outcome data, from regional and national cancer registries informing of the development of lung cancer or death from lung cancer (low-risk group).

Subjects included will be randomized prior to the initial LDCT scan. Randomization will not affect the procedure of the lung cancer screening protocol but only determine the participants

of the coronary calcium score and emphysema score reporting vs. non-reporting group. Randomization ratio of 1:1 and a 2-factorial design (¼ calc score only; ¼ emphysema score only, ¼ both; ¼ none) will provide equally sized groups of patients in the reporting and non-reporting group.

Randomization will be upheld for the one year CT screening round. Coronary calcium and emphysema scores of the subjects in the non-reporting group will remain confidential during the entire study duration (10 years).

3.3 Inclusion Criteria

1. Male and female subjects aged 55-79 years
2. Current or former smokers
3. Subjects with calculated risk score $PLCO_{2012}$ ≥1.58% (6 yrs.) or NELSON inclusion criteria (current or former smokers [those who had quit ≤10 years ago] who had smoked >15 cigarettes a day for >25 years or >10 cigarettes a day for >30 years).
4. Able and willing to give written informed consent

Volunteers fulfilling all inclusion criteria are undergoing two low dose CT screening rounds (**high-risk group**).

In addition, non-qualifying subjects fulfilling inclusion criteria 1 (age), 2 (smoking history) and 4 (consent), but do not meet the inclusion criterion 3 (risk too low) will be asked to volunteer by contributing long-term outcome data informing of the development of lung cancer or death from lung cancer (n=7100 randomly selected, **low-risk group**). These subjects will be contacted via mail after a minimum of 5 year follow up to inquire if they developed lung cancer in the time between their recruitment and present. Non-responders will be followed by local registries and by phone. New lung cancer cases will be verified using official hospital or cancer registry documents. The 5 year follow up period was chosen to account for the lead-time bias between tumor and symptoms occurrence and cancer diagnosis in the low-risk group.

3.4 Exclusion Criteria

1. Comorbidity, which would unequivocally contraindicate either screening or treatment if lung cancer were detected.
2. History of chest CT within the past year preceding the invitation.
3. Inability to undergo non-contrast CT (e.g. ≥ 200 kg body weight, inability to lie flat).
4. Pregnancy
5. Risk of non-compliance with study procedures.
    - Unable to give written consent

- Patient`s inability to fill in the questionnaire self-dependent
- Limited knowledge of the German language
- Inability to travel, residents of care facilities, etc.

4. VARIABLES AND EPIDEMIOLOGICAL MEASUREMENTS

4.1 Exposures

4.1.1 Definition of Primary Exposure

Recruited volunteers in the high-risk group undergo 2 low-dose CT screening rounds (baseline and 1 year follow up).

4.1.2 Definition of Comparison Exposure

The low-risk group will not receive low-dose CT screening. They will be contacted after 5 years to inquire if they developed lung cancer in the time between their recruitment and present. Non-responders will be followed by local registries and by phone.

4.2 Outcomes

Primary endpoints:

1. Proportion of lung cancers detected with different risk models

To address the suitability of different inclusion methods for identifying the high-risk population for screening, the $PLCO_{M2012}$ model and the NELSON inclusion criteria will be compared primarily for the positive predictive value of lung cancers detected within the study population after 2 screening rounds.

Key-Secondary endpoints:

Additionally, the $PLCO_{M2012}$ model and the NELSON inclusion criteria will be compared in a hierarchical order regarding the key secondary endpoints:

1. Proportion of individuals selected for screening within the high-risk study population
2. Proportion of lung cancers detected with different inclusion methods (NELSON vs. PLCO) within the overall study population after 5 years
3. Proportion of lung cancers detected within the high-risk population
4. Sensitivity within the overall population after 5 years.

5. Specificity within the overall population after 5 years.

Secondary endpoints:

6. **Rate of initiation of cardiovascular treatments** (in particular lipid-lowering) in the calcium score reporting group vs. the non-reporting group after year 1 of study.
7. **Efficiency of nodule management algorithms:** Based on the two alternative management algorithms (LungRads1.1 alone or LungRads1.1 + PanCan/AI) participants are sorted into three management groups: (a) next surveillance scan, (b) early recall scan, or (c) diagnostic evaluation recommended. For one algorithm to be more efficient, the following criteria must both be fulfilled
   i. The number of participants without cancer sorted in the category (a) is higher AND
   ii. The number of participants with lung cancer sorted into category (b) or (c) is higher.
8. **Success of screening program.** Based on all individuals enrolled. Definition of success is calculated using:

a. Response rate (1. Respondents to questionnaire / invitation: those who send their smoking history & other relevant data; 2.among the above respondents, those who are eligible by one of the two criteria, or both; 3. those who are eligible, and actually take part in the screening), number of drop-outs, effectiveness of patient recruitment via mailings vs. GPs referrals (individual response rates)

b. Reliability of PLCO risk scoring (self-reported vs. on site assessment)

c. Percentage of subjects receiving an adequate low-dose CT scan and report according to DRG guidelines (number of diagnostic CTs/number of all CTs)

d. Percentage of subjects receiving adequate follow-up procedures

9. **Quality of screening program.**

a. CT reading performance (2^{nd} reader vs. CAD vs. AI, positive predictive value)

b. Quality of lung nodule management

c. Frequency of detection and management of incidental findings from low dose chest CT (emphysema, coronary heart disease, etc.)

d. LDCT dose management

10. **Smoking cessation**

a. Success of smoking cessation counseling based on number of participants quitting with or without revealing additional health risks (emphysema score, coronary calcium score or both).

11. **Blood-based and exhalation-based biomarkers**

a. Evaluation of various blood-based or exhalation-based biomarkers in positive LDCT cases with subsequent biopsy on the positive predictive value of the LDCT test:

Liquid Biopsy:

- Epigenetic Signature Profile from cell free DNA (currently 835 loci), a more specific description is possible after patent approval.

Exhaled Breath Condensates:

- RNA Analysis of the genes TUBA1A and HPRT, followed by analysis for GATA6 Em, GATA6 Ad, NKX2-1 Em, NKX2-Ad.

12. **Cost-effectiveness analysis**

a. Cost-effectiveness modeling to investigate the impact of different components of LDCT lung cancer screening on the log-term all-cause mortality and cost-effectiveness: Key components include risk score-based selection criteria, nodule management protocols, threshold values of imaging biomarkers for cardio-vascular diseases and COPD, and inclusion of smoking cessation programs (CHERH).

b. Comparison of patient recruitment strategies: Cost-effectiveness of register-based mailing campaign vs. GP referrals in terms of recruitment of qualified screening subjects (CHERH).

4.3 Other Variables and Covariates

Additional primary endpoint (longitudinal follow up, not part of this study - application for additional funding after successful completion of the 2nd screening round):

1. All cause mortality rates and major adverse cardiovascular event (MACE: nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death) rate in the reporting group vs. non-reporting group at year 5 and year 10.

2. Long-term smoking cessation rates in the emphysema reporting group vs. non-reporting group at year 5 and year 10.

5. STATISTICAL ANALYSIS PLAN

5.1 Statistical Methods – General Aspects

5.1.1 Primary and key-secondary Objective(s):

The primary and key-secondary endpoints of this study will be calculated from the following two fourfold tables summarizing the distribution of included patients and patients with detected lung cancer:

Table 1

Number of Participants by Screening Eligibility			
		NELSON	
		+	-
$PLCO_{m2012}$	+	A	B
	-	C	D*

Table 2

Number of detected lung cancers by Screening Eligibility			
		NELSON	
		+	-
$PLCO_{m2012}$	+	a	b
	-	c	d*

Please note that * indicates patients with a low risk score, which are both PLCO and LLP negative at inclusion.

PPV

PPV NELSON = (a+c) / (A+C); PPV PLCO = (a+b) / (A+B).

Proportion of lung cancer detected

Secondarily, proportion of lung cancers detected will be calculated as prop_lung(PLCO) = (a+b) / (a+b+c+d*) and prop_lung(NELSON) = (a+c) / (a+b+c+d*).

Additionally, also the proportion of lung cancers detected in the identified high-risk population (PLCO or NELSON positive) will be calculated, using (a+b+c) as denominator and the proportion of individuals selected for screening within the low-risk population will also be calculated using (A+B+C+D*) as a denominator.

Proportion of individuals selected for screening

The proportion of individuals selected for screening (within the high-risk population) will be calculated as prop_screening(PLCO) = (A+B) / (A+B+C) and prop_screening(NELSON) = (A+C) / (A+B+C) .

Specificity

Specificities of the risk scores will be calculated as spec(PLCO)=(C+D* – c-d)/(A+B+C+D* – a –b-c-d*) and spec(LLP)=(B+D* – b-d*)/(A+B+C+D* – a –b-c-d*).

Sensitivity

The sensitivities correspond to the proportions of lung cancer detected in the overall population.

The primary and key-secondary endpoints will be compared between PLCO score and NELSON inclusion criteria in a hierarchical at a two-sided type-I-error of 5% to control the overall type-I-error at 5% (according to the hierarchy of endpoints outlined above). As the primary analysis, for testing the null-hypothesis of no difference between the risk scores regarding the proportion of lung cancers detected, McNemar's Test will be used.

Statistical testing

For testing the null-hypothesis of equal positive predictive values, the weighted generalized score statistic developed by Kosinski et al. (20) will be used.

For testing the null-hypothesis of no difference between the risk scores regarding the proportion of individuals selected for screening, McNemar's Test will be used.

Description of the primary analysis and population:

The primary analysis will be conducted of all volunteers within the overall study population after 2 LDCT screening rounds.

5.1.2 Secondary Objective(s): Calculation of Epidemiological Measure(s) of Interest (e.g. hazard ratios, incidence rates, test/retest reliability)

1. Rate/rate ratio of initiation of cardiovascular treatments (in particular lipid-lowering) in the calcium score reporting group vs. the non-reporting group after year 1 of study:

2. Efficiency of nodule management algorithms:

Based on the two alternative management algorithms (LungRads1.1 alone or LungRads1.1 + PanCan) patients are sorted into three management groups: (a) next surveillance scan, (b) early recall scan, or (c) diagnostic evaluation recommended. For one algorithm to be more efficient, the following criteria most both be fulfilled

i. The number of patients without cancer sorted in the category (a) is higher AND

ii. The number of patients with lung cancer sorted into category (b) or (c) is higher.

3. Success of screening program. Based on all individuals enrolled. Definition of success is calculated using:

a. Response rate (number of responses/overall number contacted), number of drop-outs, effectiveness of patient recruitment via mailings vs. GPs referrals (individual response rates)

b. Percentage of subjects meeting all inclusion/exclusion criteria

c. Repeatability of the PLCO score

d. Percentage of subjects receiving an adequate low-dose CT scan according to DRG guidelines (number of diagnostic CTs/number of all CTs)

4. Quality of screening program.

a. CT reading performance (2^{nd} reader vs. CAD vs. AI)

b. Frequency of detection and management of incidental findings from low dose chest CT (emphysema, coronary heart disease, etc.)

c. Subsequent identification of biomarkers with predictive value / correlation with positive LDCT findings / cancer risk

5. Smoking cessation

a. Success of smoking cessation counseling based on number of participants quitting with or without revealing additional health risks (emphysema score, coronary calcium score or both).

6. Blood-based and exhalation- based biomarkers

a. Evaluation of various blood-based or exhalation- based biomarkers in positive LDCT cases with subsequent biopsy on the positive predictive value of the LDCT test.

7. Cost-effectiveness analysis

a. Cost-effectiveness modeling comparing screening costs and mortality benefits from lung cancer, cardiovascular and all-cause mortality (performed by Center for Health Economics Research Hannover (CHERH, DZL funding)

b. Comparison of patient recruitment strategies: Cost-effectiveness of register-based mailing campaign vs. GP referrals in terms of recruitment of qualified screening subjects (CHERH, DZL funding).

5.1.3 Exploratory Objective(s): Calculation of Epidemiological Measure(s) of Interest (e.g. hazard ratios, incidence rates, test/retest reliability)

Additional primary endpoint (longitudinal follow up, not part of this study - application for additional funding after successful completion of the 2nd screening round):

1. Mortality rates and major adverse cardiovascular event (MACE) rate in the reporting group vs. non-reporting group at year 5 and year 10 (not part of this funding period).

2. Long-term smoking cessation rates in the emphysema reporting group vs. non-reporting group at year 5 and year 10 (not part of this funding period).

5.2 Bias

5.2.1 Methods to Minimize Bias

Randomization: Subjects included in the screening study will be randomized prior to receiving the initial LDCT scan. Randomization will not affect the procedure and the schedule of the cancer screening process but only determine the allocation of the participants of the coronary calcium score and emphysema score to the reporting and the non-reporting group. Randomization ratio of 1:1 and a 2-factorial design (¼ calcium score only; ¼ emphysema score only, ¼ both; ¼ none) will provide equally sized groups of patients in both groups including age and sex stratification.

Sampling bias: To minimize sampling bias we randomly select volunteers in the age group 55-79 from the local general population registry database ("Einwohnermeldeämter") to be contacted via mail at each study center. Additional recruitment efforts via GP or public media may introduce a sampling bias; however, this recruitment strategy reflects the real world setting of a future German national lung cancer-screening program. Additionally, we will track and analyze the recruitment pathways in the HANSE study.

5.2.2 Adjustment for Multiple Comparisons

The primary end key-secondary endpoints will be tested in a hierarchical order, thereby controlling the overall type-I error rate at 5%. Therefore, no correction of p-values for multiple testing needs to be performed. All secondary parameters will be considered explorative.

Strengths and Limitations

Strengths

Importantly, the results and the innovative workflow infrastructure of this study should pave the way for an effective comprehensive screening program in Germany. Especially, novel results about the definition of the high-risk population, the inclusion of cardiovascular and lung comorbidity, smoking cessation and cost-effectiveness will guide the future German lung cancer screening program.

Limitations:

This study is designed as a reference case for a nationwide lung cancer screening program, which both suffer from limitations. The voluntary participation may introduce a certain bias and may not reveal all high-risk cases. In addition, clinically not apparent lung cancer cases in the low-risk population will be missed, since this group will not receive a LDCT. However, we follow-up smokers, who did not meet the risk score inclusion criteria and were willing to participate in the study, after 5 years to calculate the proportion of clinically detected lung

cancers, which were missed due to non-inclusion in the high risk group. This will generate important data for the ethical and economical discussion of risk-based inclusion for lung cancer screening.

The assessment of coronary calcium scores is usually performed on normal dose ECG-gated CT. However, recently it has been shown that coronary artery calcium scoring is feasible on non-ECG-gated LDCT. Furthermore, the used Coreline software has an innovative and fully automated algorithm especially developed for non-ECG gated Coronary calcium score on LDCT.

Due to the 36 month time horizon of the study, the endpoint 'initiation of cv treatment' was selected, rather than a clinically more meaningful endpoint, such as 10 year cardiovascular mortality, for example. However, the investigators will seek additional funding to continue the coronary calcium part of the study in order to evaluate cardiovascular and all-cause mortality at year 10 follow-up.

5.3 Sample Size and Power Calculations

To be assessed for eligibility: **n = 350 000**

To be allocated to trial: **n = 5500 + all recruited volunteers with low risk scores/low NELSON criteria (low risk group)**

To be analysed: **n = 5000 + 7100 low risk group**

(i) **Power calculation for the primary endpoint**

Sample size calculation is based on data from the German Health Update study (GEDA; "Gesundheit in Deutschland aktuell") - a health monitoring program consisting of cross-sectional surveys conducted by the Robert Koch Institute to provide data on health and disease, health determinants and health behaviors from nationally representative samples of adults in Germany (20). Between 2008 and 2013, three GEDA studies were carried out, in 2008–2009, 2009–2010 and 2012–2013, involving a total of 62,606 computer assisted telephone interviews (23, 24). Based on this dataset the PLCO risk score was adjusted to a level (5-year risk of 1.314%, or 6-year risk of 1.58% [rounded]) were the NELSON inclusion criteria and the PCLO risk score are equally weighted in the German population aged 55-79 to include the same amount of volunteers in each group (table 3)

Table 3:

Risk threshold of 0.01314 (5y risk,weighted, scaled to 5000 participants) - Eversmokers aged 55-79				
		Nelson		
		0	1	
PLCO	0	7095.8 (21.8)	1070.25 (9.8)	
	1	1072.73 (27.0)	2857.04 (112.2)	

Number of ever smokers (predicted cancers) GEDA dataset (23, 24).
Between parentheses are the 5-year case numbers predicted by the PLCO model.

In a study by Hüsing & Kaaks (24) this model was found to accurately predict absolute lung cancer incidence compared to incidence actually observed (cancer registry data).

However, for power calculations one cannot directly assume that predicted 5-year incidence corresponds to the number of LC cases that will be detected by two CT screenings over a 1-year interval.

To estimate the number of expected CT-detected cases (two screens, 1-year interval) we extrapolated from observations in the LUSI trial. LUSI included participants 50-69 years of age who met the smoking criteria of NELSON. In a total of 2029 participants in the screening arm, 34 LC cases were detected in the first two screening rounds (22 at prevalence screen, and 12 at the first incidence screen).

From GEDA data, using the PLCO model, we estimated that, compared to individuals who meet the inclusion criteria of LUSI (age 50-69, and smoking criteria identical as in NELSON) the (5-year) LC incidence is 1.72 times higher for individuals in the higher age range (55-79, + NELSON smoking criteria) chosen for the present study.

For the present study, we thus estimated an expected overall number of CT-detected cases of 144:34 x 5000/2029 x 1.72 = 144

We assume that these 144 CT-detected cases will be proportionally distributed as those in Table 3 (i.e., as with predicted 5-year incidence without screening).

The numbers in Table 3 suggest that the PPV of the PLCO (risk-based, with 6-year risk threshold of 1.58%) will be 14% higher than the PPV of NELSON.

For comparing positive predictive values from a paired diagnostic study, the weighted generalized score statistic proposed by Kosinski (20) will be used to test the Null-hypothesis of the PPVs being equal for Nelson and PLCO.
Using a two-sided type-I error rate of 5%, the power of the primary comparison was estimated with a simulation study based on the above described proportions. Assuming an overall number of 5000 patients who are selected by the Nelson or the PCLO criterion, and number of patients which are positive by Nelson or PLCO only are simulated as a realization of a multivariate variable with n=5000 and proportions (2857/5000, 1070/5000 and 1072/5000 respectively) as

n_both, n_Nelson and n_PLCO. Subsequently, the number of cancers detected was calculated from independent Binominal variables for each of the following conditions.

Number of cancers in the group of patients who are Nelson and PLCO positive: Bin(n_both, (144/149)*(112/2857))
Number of cancers in the group of patients who are Nelson positive and PLCO negative: Bin(n_Nelson, (144/149)* (10/1070))
Number of cancers in the group of patients who are Nelson negative and PLCO positive: Bin(n_PLCO, (144/149)* (27/1072))

The empirical power was estimated as the proportion of 10,000 simulation runs, where the weighted generalized score statistic (20) applied to the simulated data showed a p-value smaller than 5%.

Based on the above procedure, the estimated power to reject the null-hypothesis of equal PPVs between the NELSON and the PLCO score is 80,3%.

For the HANSE study the calibrated threshold for the PLCO 5 year risk score of 1,314% was converted to a 6year threshold of 1,58% , because the original PLCO risk score calculates the 6year risk and thus the original calculators by Tammemägi et al. can be used for the HANSE study (13).For this conversion linearity between year 5 and 6 was assumed.

(ii) Sample size for the evaluation of **initiation of cardiovascular therapy** within 1 year after randomization has been calculated using Chi-Square Test and two-sided type-I-error rate of 5% based on the results of the ITALUNG study (15,16), where for 44% of all patients coronary artery calcification (CAC) was detected. In the ITALUNG study, 63% of patients with CAC were on cardiovascular treatment without receiving results of their low dose CT screening. For this study, where the patients are randomized to either reporting or non-reporting of CT screening results, we conservatively assume that the non-reporting group shows a rate of cardiovascular treatment of 68%. In contrast, as an effect of reporting the screening results, we assume that in the reporting group 73% of patients receive cardiovascular treatment, so the effect of reporting the CT results is assumed to be an increase of 5 percentage points in the cardiovascular treatment rate. Acknowledging that only 44% of all patients are assumed to show CAC on low dose CT, the expected difference between the reporting and non-reporting group is (73%-68%) * 44% = 2.2%. Equivalently, the assumed rate ratio between the reporting and non-reporting group is (73% * 44%) / (68% *44%) = 1.07. With 2,500 patients randomized to each arm and using a Chi-Square Test with a two-sided type-I-error rate of 5% for testing the null-hypothesis of no difference between the groups, the statistical power is 97%.

(iii) To evaluate the power of potential **longitudinal follow-up** studies based on this screening trial, the power for the 10 year mortality endpoint has been calculated based on the results of the NELSON study using a Chi-Square Test with a two-sided type-I-error rate of 5% for testing the null-hypothesis of no difference in 10-year cardiovascular mortality rates between the

reporting and non-reporting groups. In line with the results of the NELSON study, we assume a 10 year cardiovascular mortality rate in the non-reporting group of 2.7%.

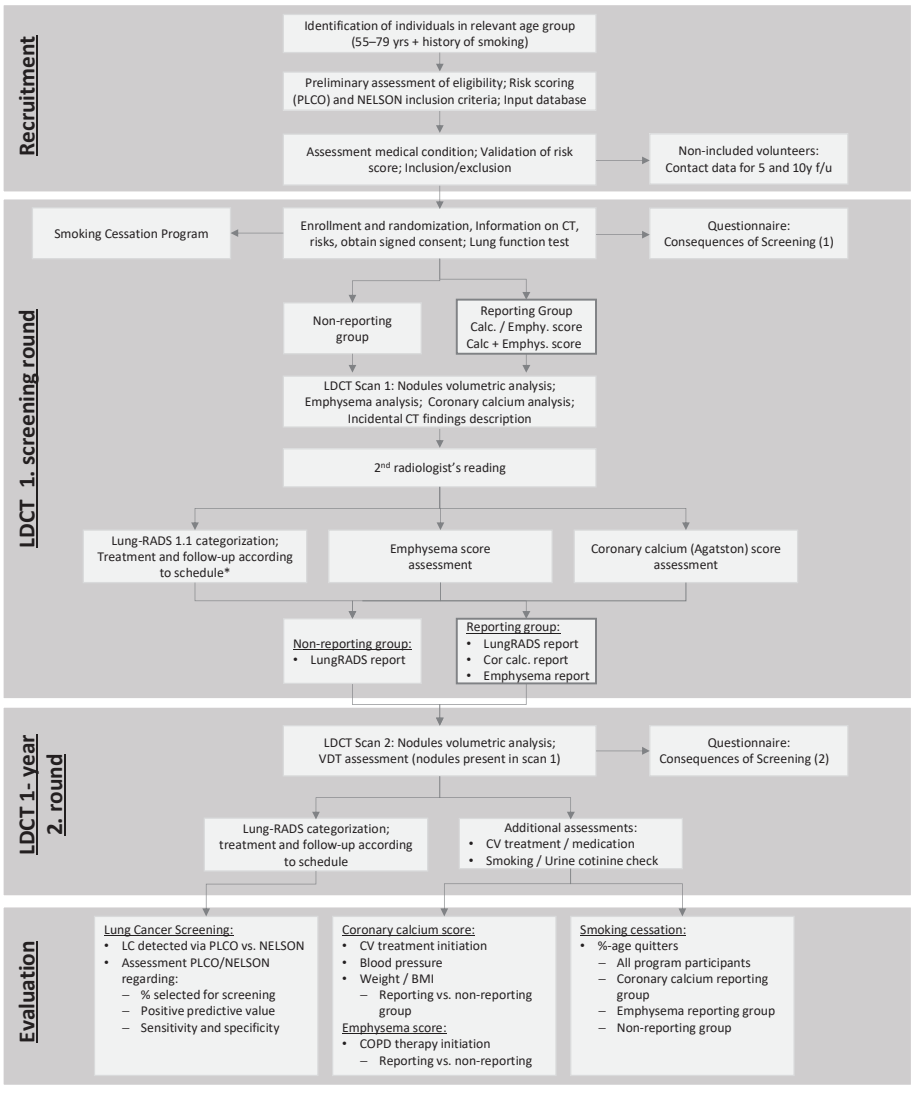
Assuming a rate ratio of 0.6 between the reporting and non-reporting group (or equivalently, a 10-year mortality rate of 1.6%), the difference between the reporting and non-reporting group can be shown with a power of 75%.

Conclusion: With an overall sample size of 5,000 subjects (and 2,500 volunteers randomized to the reporting and non-reporting group) the study is well-powered to investigate the primary hypothesis, evaluate potential cardiovascular benefit and provide the basis to investigate mortality in a follow-up study.

6. STUDY CONDUCT AND REGULATORY DETAILS

6.1 Data Management

6.1.1 Study Flow Chart and Plan



*** Follow-up schedule**

LungRADS Categories:

- 1, 2: 1 year LDCT
- 3: 6 months LDCT; VDT assessment
- 4a: 3 months LDCT; VDT assessment
- 4b, X: MDT, tissue sampling depending on the probability of malignancy and comorbidities.

Figure 1: Flow diagram of the HANSE study.

6.1.2 Procedures

Workflow Hanse Studie 1.3.pdf

Figure 2: Procedure workflow of the Hanse Study

1. **Recruitment**

- Population will be contacted by mail (address data of individuals in the age group obtained from local population registries) with an **individually tailored invitation letter** and response element (paper and website) to assess their overall qualification and willingness to participate. Additional recruitment efforts via local physicians (**GPs**), and via **public media** using the study website.

Age	
Gender	
Race/ethnicity	
Education	
Height	
Weight	
Chronic obstructive pulmonary disease (yes vs. no)	
Prior diagnosis of pneumonia (yes vs. no)	
Prior diagnosis of emphysema (yes vs. no)	
Prior diagnosis of bronchitis (yes vs. no)	
Prior diagnosis of tuberculosis (yes vs. no)	
Personal history of cancer (yes vs. no)	
Family history of lung cancer (yes vs. no)	
Early onset vs. late onset	
Smoking status (former=0, current=1)	
Former smoker (yes vs. no)	
Current smoker (yes vs. no)	
Smoking intensity (average cigarettes/day)	
Smoking duration (years)	
Smoking quit-time	
Chest CT within past year (yes vs. no)	
Pregnancy yes/no	
Any comorbidities (free text)	
Ability to travel to the screening center	

Table 5: Variables for risk scoring, applicable for PLCO model

- Initial eligibility assessment based on self-reported data (age, smoking history and parameters required for the NELSON inclusion criteria and PLCO scores, table 5) in return letter, based on individuals' input in study website, or according to GP assessment. Data of eligible subjects will be stored in CRO database. Eligible subjects (based on initial assessment of risk) will receive an invitation for participation in the screening program with additional background information.

- On site validation of variables required for risk scoring models and accompanying assessment of medical condition, medical history, current medication by qualified medical staff.

- Data will be stored in database (CRO) and $PLCO_{M2012}$ risk score and NELSON inclusion criteria will be determined. Individuals with $PLCO_{M2012}$ risk score ≥1.58% (6 yrs.) or NELSON inclusion criteria will be included in the study.

- Non-qualifying subjects (who did not meet the NELSON inclusion criteria or PLCO criteria) will be asked to volunteer by contributing long-term outcome data informing of the development of lung cancer or death from lung cancer. In addition NELSON and PLCO non-qualified subjects with a smoking history, who volunteered to participate in the HANSE study, will be contacted via mail after 5 years to inquire if they developed lung cancer in the time between their recruitment and present. Non-responders will be followed by local cancer registries and by phone.

2. **LDCT - 1. Screening round**

- **Lung function test:** All included participants will receive a lung function test prior to undergoing LDCT.

- **Cardiovascular health**: All participants will be questioned whether they receive treatment for any cardiovascular conditions. Blood pressure, heart rate and BMI data (height and weight) will be obtained.

- Assessment of current **COPD treatment medication**.

- **Randomization:** Subjects included in the screening study will be randomized prior to receiving the initial LDCT scan. Randomization will not affect the procedure and the schedule of the cancer screening process but only determine the allocation of the participants of the coronary calcium score and emphysema score to the reporting and the non-reporting group. Randomization ratio of 1:1 and a 2-factorial design (¼ calcium score only; ¼ emphysema score only, ¼ both; ¼ none) will provide equally sized groups of patients in both groups including age (5 year groups) and sex stratification .

Lung LDCT assessment:

- **Standardized and quality-assured image analysis** will be conducted using state-of-the-art artificial intelligence (AI)-based detection and nodule measurement software (Coreline) to support the radiologist. CT assessment of lung nodules will be performed according to LungRADS 1.1 criteria (see Appendix), as well as volume doubling time according to the European position statement on lung cancer screening (14).

- Inspection of **lungs for nodules** will be carried out for all subjects, independent of the assigned groups (reporting or non-reporting).

- An independent 2nd read by an additional radiologist using the same reading software algorithm will be performed.

- Subjects with no nodules or those of LungRADS grades 1, 2, 3, 4a will be scheduled for follow-up scans at intervals according to LungRADS schedule (see Appendix).

- Findings categorized as LungRADS Cat. 4b or 4X nodules will be presented to the local Multidisciplinary Tumor Board (MDT) for further assessment and treatment decisions in the clinical routine workflow.

- **Emphysema** severity as a measure for tobacco related lung destruction will be quantitatively assessed on the LDCT images using the fully automated artificial intelligence (AI)-based algorithm of the Coreline software (Coreline, Seoul South Korea). The data will either be reported to study participants and treating physicians or not according to the allocation of the individual to the two randomized experimental groups.

- **Coronary calcium scores** (Agatston score) will be assessed using the fully automated artificial intelligence (AI)-based algorithm of the Coreline software (Coreline, Seoul South Korea). However, only the reporting group will receive the results of the score, together with an explanation of potential consequences of these findings for their cardiovascular health and with recommendation to seek specific consultation with their general practitioner or specialist. In this group a report is sent to the participants' GP.

- The LDCT image data, the coronary calcium score and % emphysema of the non-reporting group will remain confidential and will be stored for further assessment at year 1 (follow-up CT screen) and for evaluation of endpoints at year 5 and 10 (not part of this funding period).

- Apart from the randomized reporting of coronary artery calcium score and % emphysema **clinically relevant incidental findings** will be categorized in emergent (within 1-30 days), timely (within 1-6 months) or regular (>6 months) follow up. They will always be included in the CT report for the study participants.

- For emergent findings the study participant will be contacted directly by the local study team.

- Clinically non-relevant CT findings (i.e. liver or kidney cysts) not requiring physician consultation will not be included in the report.

Smoking cessation program:

- Prior to obtaining the chest CT, all participants are counselled for smoking cessation and referred to a smoking cessation program, according to the requirements defined by the Joint Statement of the German Radiological Society. Specifically, participation in local certified smoking cessation programs such as "Das Rauchfrei Programm" (https://www.mhh.de/pneumologie/rauchfrei) is encouraged. In addition, an information brochure about smoking cessation and available local certified smoking cessation programs and further online information material will be given to each participant.

Biomarker program:

- All patients undergoing tissue sampling according to the LungRADS 1.1. criteria will be invited to participate in the translational biomarker program using a separate informed consent form. For the program, a blood sample for epigenetic profiling will be required, together with an exhalation sample for assessment of specific exhalatory transition markers. The findings of the Biomarker analysis will be correlated to the pathological results of the radiological finding. The exact biomarkers will be determined before the study start and included in the appendix of the protocol.

- Optionally, blood samples will be collected from the high-risk group at the 1st and 2nd screening round visit and stored in the DZL biobank for future research.

Long-term performance and cost-effectiveness:

- The Center for Health Economics Research Hannover (CHERH) develops a comprehensive microsimulation platform for the assessment of long-term performance and cost-effectiveness of nationwide lung cancer screening with LDCT based on the HANSE study data. Main objectives of the modelling study are to investigate the impact of different components of LDCT lung cancer screening on the log-term all-cause mortality and cost-effectiveness. Key components include risk score-based selection criteria, nodule management protocols, threshold values of imaging biomarkers for cardio-vascular diseases and COPD, and inclusion of smoking cessation programs.

- ***Model concept:*** The stochastic microsimulation model simulates virtual life histories of the HANSE study, which represents a representative sample of the German population in northern Germany. For each individual, it creates different life histories: no LC-screening, LC-screening focussing on lung cancer only, LC-screening including cardiovascular and lung comorbidity assessment, comprehensive LC-screening plus

smoking cessation program. A team of clinical and health economic experts will define the detailed structure of the model.

- ***Outcome analyses:*** For each screening scenario, a Monte Carlo simulation (MCS) with 1,000 iterations will be performed to estimate expected outcomes and MSC-based confidence intervals. Primary outcomes of the analysis are long-term all-cause mortality, additional costs per quality-adjusted life year (QALY) gained, per life year (LY) gained or per death averted. Efficiency frontiers will be constructed for each primary outcome to identify efficient screening scenarios and calculate the incremental cost-effectiveness of these scenarios. The impact of variations in the values of key input parameters (adherence to screening, smoking cessation etc.) on model outcomes will be tested in sensitivity analyses.

Consequences of screening:

- All screened individuals will ask to participate in a 'Consequences of Screening' survey in order to evaluate their emotional and psychological condition during the screening process. Survey will be based on the psychological consequences questionnaire, adapted for lung cancer screening (19).

- In addition, the patient questionnaire will evaluate the socioeconomic background, smoking cessation, lung and cardiovascular health.

- The exact questions of the questionnaire will be determined before the study start and included in the appendix of the protocol.

- GP contact information is recorded.

- Current medication is recorded.

3. LDCT 1 year - 2. Screening round

Timing of the follow-up chest CT according to LungRADS 1.1 schedule.

Chest LDCT scan procedure and image analysis as in the 1st screening round.

- **Lung LDCT assessment:** Assessment of newly identified lung nodules will be done according to LungRADS 1.1 criteria. Follow-up radiographic assessment of solid nodules will be based upon volume doubling time (VDT) as a key driver for recommendations on further course of action.

- **Lung function test:** All included participants will receive a lung function test prior to undergoing LDCT.

- **Cardiovascular health**: All participants will be questioned whether they initiated treatment for any cardiovascular conditions during the study. Blood pressure, heart rate, and BMI data will be obtained.

- Additionally, the study is designed to analyze cardiovascular events and mortality in a follow-up study at year 5 and 10 (not part of the current funding period).

- **Assessment of smoking status:** Success of the smoking cessation program will be evaluated using a questionnaire, combined with a urine cotinine check (in quitters).

- **Initiation of COPD treatment:** Assessment of COPD treatment initiation during the study.

- **Consequences of screening:** Questionnaire 'Consequences of Screening' as above.

2. Evaluation

Lung cancer screening:

- The percentage of subjects receiving an adequate low-dose CT scan according to DRG guidelines will be assessed.

- For all included participants, detection rate of lung cancers will be evaluated and categorized according to LungRADS 1.1 categories.

- Detected (proven by histopathology) lung cancers will be categorized whether they were predicted by PLCO or NELSON or both. Statistical analysis will reveal potential advantages of either risk scoring methodology.

- A retrospective analysis will compare this algorithm to the PanCan nodule algorithm vs. AI for management efficiency. Based on the two alternative management algorithms patients are sorted into three management groups: (a) next surveillance scan, (b) early recall scan, or (c) diagnostic evaluation recommended. For one algorithm to be more efficient, the following criteria most both be fulfilled

• The number of patients without lung cancer sorted in the category (a) is higher AND

• The number of patients with lung cancer sorted into category (b) or (c) is higher.

Coronary calcium score / cardio-vascular treatment initiation:

- At the 1-year follow-up visit, the rate of initiation of cardiovascular treatment (in particular lipid-lowering) will be determined, together with BMI, and blood pressure data. Data for the calcium score reporting group will be compared to those of the non-reporting group.

Smoking cessation:

- Success of smoking cessation counseling will be based on the number of participants quitting (% quitters) within study period.

- Allocation of the participants to the different experimental groups will allow determining the influence of 'reporting' of prognostic markers (percent emphysema and coronary calcium score) on smoking cessation.

All methods will be performed according to study site SOPs.

CT analysis software (Coreline) specifications:

1. Viewer function

- LCS (Lung Cancer Screening) viewer functions

■ Image display with axial, sagittal and coronal images and 3D rendering.

■ Virtual slice thickness control display function for MPR (Multi-Planar Reformat) images.

■ Semi-automatic nodule segmentation and measurement.

■ Follow-up nodule comparison, using automatic nodule position registration.

■ Quantitative feature calculation from the nodule segmentation.

■ Calculation of VDT (volume doubling time) and cancer-risk probability based on PANCAN model (Brock model).

■ Structured reporting UI based on Lung RADS v1.1, with incidental findings (S Modifier) (Can be modified to conform to German requirements)

■ Form-based report generation

- LAA (Lower Attenuation Area) viewer functions

■ Lobe-based quantitative emphysema analysis, such as LAA-950HU and Perc15.

■ Image display of axial, sagittal, coronal and 3D rendering, with LAA mask overlaid.

■ Bull's eye chart for displaying LAA distribution in lobes, which are automatically segmented.

■ Histogram analysis of lung parenchymal densities.

■ Form-based report generation

- CAC (Coronary Artery Calcification) viewer functions

■ Automatic calcification labeling and manual correction.

■ AGATSTON scoring and isotropic volume scoring.

■ Form-based report generation

- Automatic processing server (APS) engines

■ Lung nodule detection engine (CADe, for research purpose only till CE certification)

■ Lung/lobe segmentation engine for automatic nodule position determination.

■ LAA analysis engine

■ CAC analysis engine

- Worklist functions

■ Display the important results in separate columns; (Lung-RADS category, LAA-950HU, CAC, etc.)

■ Workflow management to enable double-reading capability.

■ Automatic notification of high-risk (critical) reading results.

■ Exporting results in CSV format (MS-Excel compatible)

2. Central registry function

- Anonymization of uploaded patient data.

- Web-based questionnaire (Specific requirements must be determined.)

- Collects all the reading results in the CLOUD database.

- CT dose management, using dose report from CT devices.

- Dashboard view to display all participating hospitals' information (charts and tables).

3. Additional function support further research work

- Radiomics feature generation from the segmented nodules.

- Exporting all the collected information in CSV format (MS-Excel compatible).

- Exporting nodule segmentation masks.

- Interface with 3rd-party research modules, such as nodule malignancy estimation.

4. Function be customized in the preparation phase of the HANSE study

- German language support.

- Customization to reflect German workflow.

- Customization of structured reporting for incidental findings.

- Development of web-based questionnaire system.

- Development of nodule management system including dashboard

- Interface with existing PACS, RIS and EMR

6.1.3 Quality Control

Monitoring

Offsite Monitoring using plausibility checks during data entry will be performed.

Training of Study Site Personnel

All study personnel will be trained according to the study SOPs prior to the study start.

6.1.4 Storage and Retention

Pseudonymized volunteer data will be stored in a password protected eCRF in a secure environment of the Alcedis Platform. Pseudonymized image data will be stored in a secure password protected cloud environment in Germany. Only the password secured Alcedis TRUST center has access to the clear name and the study pseudonym (Figure 2).

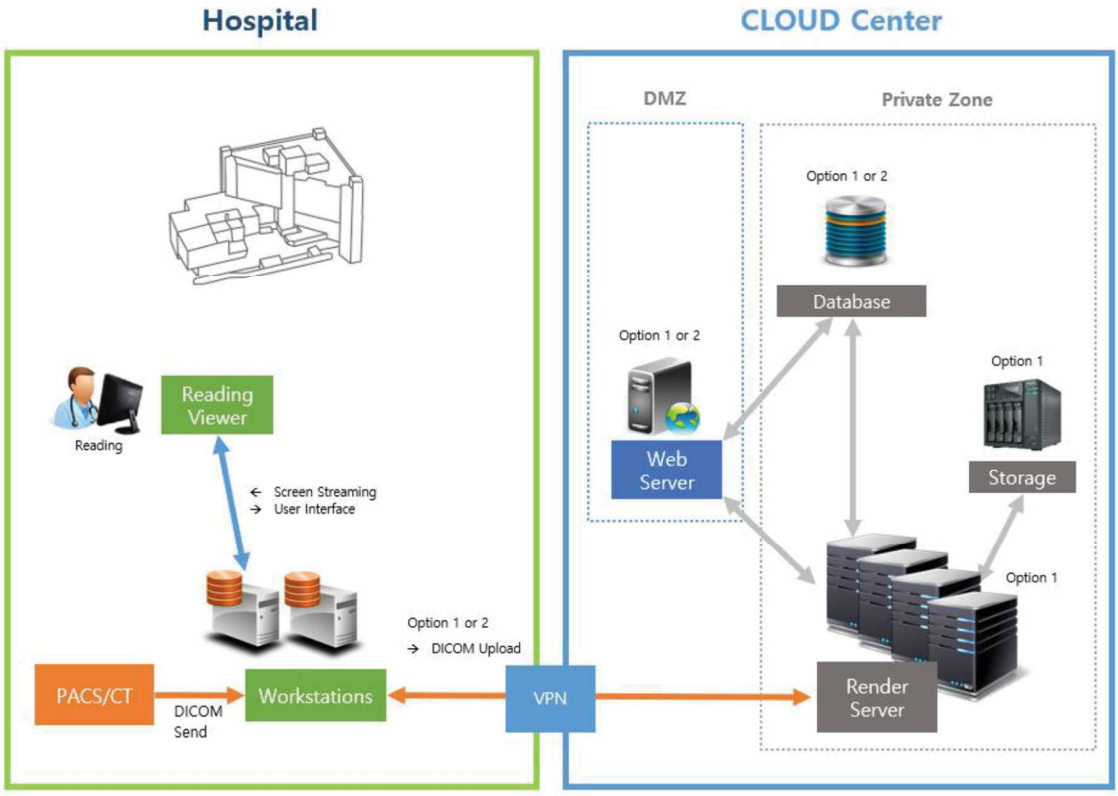


Figure 3.

For Image postprocessing and analysis the following **Hybrid system** from Coreline will be used (figure 3):

- Workstations will be installed in each hospital.

- All the DICOM CT images will be stored in the workstation of each hospital.

- Preprocessing, such as lung/lobe segmentation and nodule detection, will be done in each workstation.

- Reading doctors access their images in the workstation through their web browsers.

- Prior exams taken at a different hospital can be accessed (with one-click) in the follow-up mode from DICOM CT images in the CLOUD center.

- All the reading results (reports) are stored in the workstation first.

- All the reading results (reports) will be pseudonymized and uploaded to the secured CLOUD.

- All the DICOM CT images will be uploaded to the CLOUD (Option 1).

6.2 Protection of Human Subjects

This study will be performed in accordance with ethical principles that are consistent with the Declaration of Helsinki, ICH GCPs, GPP and the applicable legislation.

For the study procedures a patient insurance will be obtained. Once the study participant enters the clinical routine, she/he is covered by the insurance of the hospital.

6.2.1 Subject Informed Consent

Before documentation of any data, informed consent (DZL broad consent) is obtained by the patient in writing.

An unconditional prerequisite for a patient participating in the study is his/her written informed consent. Adequate information must therefore be given to the subject by the investigator before informed consent is obtained. A person designated by the investigator may give the information, if permitted by local regulations. A patient information sheet in the local language will be provided for the purpose of obtaining informed consent. In addition to this written information, the investigator or his designate will inform the patient verbally. In doing so, the wording used will be chosen so that the information can be fully and readily understood by laypersons.

The patient information sheet will be revised whenever important new information becomes available that may be relevant to the consent of patients.

The written informed consent of the patient to participate in the clinical study has to be given before any study-related activities are carried out. It must be signed and personally dated by the patient and by the investigator / person designated by the investigator to conduct the informed consent discussion. Patients are also asked to give consent to additional analysis of tumor, blood or urine material. This approval is not a precondition for participation in the study.

Provision of consent will be confirmed in the CRF by the investigator. The signed and dated declaration of informed consent will remain at the investigator's site and must be safely archived by the investigator so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. A copy of the signed and dated information and consent should be provided to the subject prior to participation.

At any time during or after the HANSE study a volunteer can withdraw from the study without any reason. In this case all collected study data will be deleted.

6.2.2 Confidentiality of Study/Subject Data

All data collected in this study will be strictly confidential in accordance with all appropriate legislation. Access to the participant files will not be permitted to anyone other than the study staff, monitors and auditors. Only the study staff involved in data collection will know the identity of the participants. Study staff will be instructed to maintain complete confidentiality of all collected data. Patient files will be kept on secure servers. The study report will not contain any patient identifying information. Participants will be assigned a unique participant number to ensure confidentiality and anonymity. Interview transcripts will be identified by this unique participant number and will not have any identifiers associated with the individual.

6.3 Management and Report of Adverse Events/Adverse Drug Reactions

6.3.1 Definition of Adverse Events (AE)

This is a population-based screening study without using medication. Low dose CT imaging will be conducted without use of contrast media, thus adverse drug reactions are not associated with the procedure. Once tissue sampling is recommended by the CT results possible adverse events due to a lung biopsy for example are part of the clinical routine workflow. Any adverse event that may have been caused by the imaging procedure or any follow-up procedure during the study will be captured and documented in the eCRF. Finally, after closure of the study, all documented events will be summarized in a line listing by the investigator.

6.3.2 Definition of Serious Adverse Events (SAE)

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions

- Is a congenital abnormality or birth defect

- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above.

6.3.3 Definition of Adverse Drug Reactions (ADR)

An ADR is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a medicinal product, suspected to be causally related to the product.

6.3.4 Collection of Adverse Events

Record all AEs with a fatal outcome in the *eCRF*.

For each AE the following variables will be collected;

- AE (verbatim)
- The date when the AE started and stopped
- Whether the AE is serious or not
- Investigator causality rating against the medicinal product (yes or no)
- Action taken with regard to medicinal product
- Outcome

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Sections 6.3.1 to 6.3.3 above. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets one of the criteria shown in Section 6.3.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE if it satisfies one of the criteria shown in Section 6.3.2.

Any AE which is not required to be collected, as specified in the protocol, can be reported according to local regulations.

Causality collection

The Investigator will assess the causal relationship between study procedures and each Adverse Event, and answer ‘yes’ or ‘no’ to the question ‘Do you consider that there is a reasonable possibility that the event may have been caused by the study procedure?’

Time period for collection of adverse events

Adverse Events will be collected from time of the 1st screening round visit *and during any follow-up period specified in the protocol*.

6.3.5 Reporting of Adverse Events

All SAEs will be reported, whether or not considered causally related to the study procedure(s). The reporting period for SAEs is the period immediately following the time that written informed consent until the end of the HANSE study (eCRF closure). The investigator is responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

6.4 Communication Plan

The results of the study will be published in peer-reviewed journals shortly after study-finalization, independently of a positive or negative overall study result. All scientifically involved participants of the study will be considered as authors in the respective trial publications according to the guidelines of the International Committee of Medical Journal editors (http://www.icmje.org/).

Importantly, the results and the innovative workflow infrastructure of this study should pave the way for an effective comprehensive screening program in Germany. Especially, novel results about the definition of the high-risk population, the inclusion of cardiovascular and lung comorbidity, smoking cessation and cost-effectiveness will guide the future German lung cancer screening program.

Outreach to the general public and smokers a study web presence will be designed and implemented during the first 3 months of project commencement and updated regularly and augmented via the use of social media. This public website will act as an information point for the work of the project providing details of all innovative, scientific, translational and socioeconomic aspects of the HANSE study, thus benefitting future studies in respiratory medicine, cardiology and oncology. Information will be communicated both on a general and a specialized level in order to specifically address different target groups. It is planned to link the site to patient smoking cessation groups and regional general practitioner networks. A leaflet including basic information about the project will be produced and used for both digital and printed communication/information material. The general public will also be addressed via publications/press releases, videos and social media.

Targeted stakeholder information

In order to enable a two-way dialogue with stakeholders on objectives and results of the HANSE-study, these will be presented to physicians at conferences such as the annual meetings of the Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie, Deutsche Gesellschaft für Pneumologie, Deutsche Röntgengesellschaft. Importantly, the Gemeinsamer Bundesausschuss (GBA) will be approached with the results of the HANSE study in order to initiate and improve a national cost effective and holistic interdisciplinary lung cancer-screening program in Germany.

6.4.1 Publication Plan

2021 Study design paper

2022 Radiology paper (s)

2023 HANSE study paper, Cost effectiveness modelling paper

6.4.2 Compliance with Study Registration and Results Posting Requirements

Study information from this study protocol will be posted on clinicaltrials.gov before enrolment of subjects begins.

A permission to use LDCT in this study protocol will be obtained from the Bundesamt für Strahlenschutz (BfS).

In Germany where reference to an Independent Ethics Committee (IEC) is required, documented approval from appropriate IECs will be obtained prior to study start. When necessary, an extension, amendment or renewal of the IEC approval must be obtained.

6.4.3 Compliance with Financial Disclosure Requirements

All investigators will comply with the financial disclosure requirements.

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8. APPENDICES

LungRADS 1.1 Classification system

https://www.acr.org/-/media/ACR/Files/RADS/Lung-RADS/LungRADSAssessmentCategoriesv1-1.pdf

LungRADS v 1.1.pdf

LungRADS 1.1 classification will be used, except for the "Growth" definition. Lung nodule growth in the HANSE study will be defined according to the NELSON study (6) as:1. Volume doubling time (VDT) < 400 days (positive) is suspicious for malignancy with further nodule workup as per MDT decision.

2. VDT of 400-600 days (intermediate) results in repeat LDCT scan in 3 months.

3. VDT>600 days: continue annual screening.

9. ATTACHMENTS

Patient information sheets / informed consent forms will be submitted as stand-alone documents.
Patient questionnaires will also be submitted as stand-alone documents.