Lung cancer screening using low-dose computed tomography[1]

EXTRACT

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Key statement

Research question

Research question 1: Update of benefit assessment S19-02

As an update of IQWiG report S19-02, the aim of this investigation is to assess the benefit of lung cancer screening using low-dose computed tomography (CT) versus no (or no systematic) screening. The target population is current and former smokers without suspected lung cancer.

Research question 2: Benefit assessment of variants of lung cancer screening

The aim of this investigation is to assess the benefit of variants of lung cancer screening using low-dose CT based on informative randomized controlled trials (RCTs) that at least address the following aspects: screening intervals, technical equipment standards, performance of image evaluation, and algorithms for clarifying abnormal or equivocal test results. The target population is people without suspected lung cancer or with test results requiring clarification based on previous imaging as part of a screening test.

Conclusion

Research question 1: Update of benefit assessment S19-02

For the update of report S19-02, 2 additional documents with usable data from 2 RCTs already included in report S19-02 were identified (LUSI and UKLS). Overall, results from 9 studies were thus available for the benefit assessment of screening for lung cancer using low-dose CT versus no screening.

After updating the analyses, there was still no hint of a benefit of low-dose CT screening versus no screening for overall survival.

After updating the analyses, there is proof of a benefit of low-dose CT screening for lung cancer-specific mortality. Compared with report S19-02, the certainty of the conclusions for this outcome was upgraded from an “indication” to “proof” based on the new evidence.

The results continue to support the previous assumption that screening also has a positive effect on all-cause mortality. The respective estimates and the associated confidence intervals for the absolute effect on all-cause mortality and lung cancer-specific mortality are of a similar magnitude. Considering these two mortality outcomes together therefore provides an indication of a benefit of low-dose CT screening for the outcome of mortality. Thus, overall the certainty of conclusions for this outcome was upgraded from a “hint” to an “indication” compared with report S19-02.

No new data were reported for adverse events (AEs) and consequences of incorrect screening results. Therefore, based on the analyses in report S19-02, the conclusions about the evidence

for these outcomes remain unchanged: For AEs, there is a hint of harm from low-dose CT screening. For “consequences of incorrect screening results”, there is proof of harm from low-dose CT screening based on the results for consequences of false-positive screening results.

After updating the analyses, as in report S19-02, there is proof of harm from low-dose CT screening for the outcome of overdiagnosis.

As in report S19-02, there are no usable data for the outcome of health-related quality of life.

The new data from 2 studies identified in the update further substantiated the benefit of low-dose CT screening for the outcome of mortality. The proof of harm from low-dose CT screening in terms of overdiagnosis still remains after the update of the results, but this does not call into question the indication of a benefit of low-dose CT screening for mortality. In summary, the data show that there is an indication of a benefit of low-dose CT screening versus no screening and that the benefit of low-dose CT screening outweighs harm in (former) heavy smokers. This leads to a change in the overall conclusion compared with the assessment of report S19-02. The certainty of conclusions was upgraded from a “hint” to an “indication”.

Research question 2: Benefit assessment of variants of lung cancer screening

There was only 1 study for the benefit assessment of variants of lung cancer screening. It compared screening intervals of different lengths (biennial versus annual low-dose CT screening). Therefore, the assessment of variants of low-dose CT screening was limited to the aspect of the frequency of screening and was restricted to the variants of annual and biennial screening.

For the outcomes of mortality, AEs, consequences of false-positive screening results and overdiagnosis, there was no hint of a greater benefit or greater harm from biennial versus annual low-dose CT screening. No data were available on the outcomes of consequences of false-negative screening results and health-related quality of life. In the overall assessment across outcomes, therefore no hint was derived with regard to a greater benefit or greater harm of biennial versus annual low-dose CT screening.

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
AHRQ	Agency for Healthcare Research and Quality
BfS	Bundesamt für Strahlenschutz (Federal Office for Radiation Protection)
BMUV	Bundesministerium für Umwelt, Naturschutz und nukleare Sicherheit und Verbraucherschutz (Federal Ministry for the Environment, Nature Conservation and Nuclear Safety and Consumer Protection)
CI	confidence interval
CT	computed tomography
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HTA	health technology assessment
IDR	incidence density quotient
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention to treat
LLPv2	Liverpool Lung Project Version 2
RCT	randomized controlled trial
StrlSchG	Strahlenschutzgesetz (Radiation Protection Act)
USPSTF	U.S. Preventive Services Task Force

1 Background

IQWiG report S19-02 found a hint of a benefit of screening for lung cancer using low-dose computed tomography (CT) versus no screening. For (former) heavy smokers, this means that the benefit of low-dose CT screening outweighs the harm [1]. As ionizing radiation is used in this screening test, §84 (3) of the German Radiation Protection Act (StrlSchG) [2] requires that its use has been permitted. In July 2023, the Federal Ministry for the Environment, Nature Conservation, Nuclear Safety and Consumer Protection (BMUV) published a draft bill on the "Ordinance on the permissibility of the use of low-dose computed tomography for screening for lung cancer in smokers" for comment. The basis for the decision was the scientific assessment published by the Federal Office for Radiation Protection (BfS) in December 2021 [3]. Now that the BMUV's draft ordinance is available, the Federal Joint Committee (G-BA) is initiating the consultation procedure on the introduction of screening for lung cancer using low-dose CT for active and former smokers. As soon as the BMUV ordinance becomes legally binding, the prerequisites for the use of this type of screening will be in place. The screening test can thus be offered as an individual health care service and, following a decision by the G-BA on the inclusion of the test in the catalogue of health care services provided by statutory health insurance, can be offered as part of a national screening programme [4].

The epidemiology and pathophysiology of the groups of people concerned have already been described in report S19-02 [1]. The benefit assessment has shown that (former) heavy smokers can benefit from low-dose CT screening. The screening studies included in the S19-02 report showed considerable heterogeneity in terms of screening and diagnostic strategies [1]. This concerned aspects such as the classification and definition of the screening results, the follow-up and confirmatory diagnostics after an abnormal result, the types of CT equipment used or the software-aided diagnostic evaluation. It is therefore also of interest to find out which variants of low-dose CT screening are most suitable.

On 23 November 2023, the G-BA commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess screening for lung cancer using low-dose CT. The assessment was to be carried out as an update to IQWiG report S19-02 [1]. In addition, variants of low-dose CT screening were to be compared.

2 Research question

2.1 Research question 1: Update of benefit assessment S19-02

As an update of IQWiG report S19-02, the aim of this investigation is to assess the benefit of lung cancer screening using low-dose CT versus no (or no systematic) screening. The target population is current and former smokers without suspected lung cancer.

2.2 Research question 2: Benefit assessment of variants of lung cancer screening

The aim of this investigation is to assess the benefit of variants of lung cancer screening using low-dose CT based on informative randomized controlled trials (RCTs) that at least address the following aspects: screening intervals, technical equipment standards, performance of image evaluation, and algorithms for clarifying abnormal or equivocal test results. The target population is people without suspected lung cancer or with test results requiring clarification based on previous imaging as part of a screening test.

3 Methods

The benefit assessment of lung cancer screening using low-dose CT versus no (or no systematic) screening is an update of IQWiG report S19-02.

For research question 1, current or former smokers without suspected lung cancer formed the target population of the benefit assessment. The test intervention was screening for lung cancer using low-dose CT. The control intervention was no (or no systematic) screening. Screening for lung cancer by means of chest X-ray was also considered as a control intervention in the sense of a sensitivity analysis for the outcomes of mortality and overdiagnosis.

For research question 2, the target population for the benefit assessment was people without suspected lung cancer and people with a test result requiring clarification, i.e. after previous imaging as part of a screening test. The test intervention was screening or confirmatory diagnostics for potential lung cancer using low-dose CT. The control intervention was screening or confirmatory diagnostics for potential lung cancer using low-dose CT in a different variant than the test intervention.

The following patient-relevant outcomes were considered for both questions:

- Mortality (all-cause mortality, lung cancer-specific mortality),
- Morbidity (e.g. cancer-related symptoms),
- Health-related quality of life,
- Adverse effects such as harm resulting from the screening test or from subsequent diagnostic tests (e.g. invasive procedures such as biopsies), including the consequences of incorrect screening results (false positive and false negative) and overdiagnosis.

For both research questions, only RCTs were included in the benefit assessment. There were no restrictions regarding the duration of the studies.

As part of the preparation of the rapid report, a search for systematic reviews was carried out in the MEDLINE database (including the Cochrane Database of Systematic Reviews) and the

HTA Database, as well as on the websites of the National Institute for Health and Care Excellence (NICE) and the Agency for Healthcare Research and Quality (AHRQ).

The information retrieval follows on from the previous benefit assessment S19-02 [1] and was supplemented by a systematic search for relevant studies or documents for the period not covered in the final report S19-02.

The systematic literature search for studies was carried out in the MEDLINE, Embase and Cochrane Central Register of Controlled Trials databases.

In addition, the following information sources were considered: study registries, documents submitted by the G-BA, and reference lists of identified systematic reviews. For research question 2, references were screened that had been excluded for report S19-02 (exclusion reason “E1: population” and “E3: control intervention”; see Table 5 of the full report).

The selection of relevant studies was carried out by 2 persons independently of each other. Discrepancies were resolved by discussion. Data were extracted into standardized tables. Across-outcome and outcome-specific risk-of-bias criteria were evaluated to assess the qualitative certainty of results (shortened to “certainty of results” in the following text), and the risk of bias was rated as low or high in each case. The results of the individual studies were described according to outcomes.

In addition to the comparison of the results of the individual studies, meta-analyses and sensitivity analyses were performed and effect modifiers examined, provided that the methodological requirements were met.

If new documents on studies already extracted in report S19-02 were available, it was checked whether more recent results could be used from the new publications. The results from meta-analyses were updated taking into account the available data from S19-02 and the newly identified data for rapid report S23-02.

For each outcome, a conclusion on evidence of (greater) benefit and (greater) harm was made in 4 grades regarding the respective certainty of conclusions: either proof (highest certainty of conclusions), an indication (moderate certainty of conclusions), a hint (weakest certainty of conclusions), or none of these 3 situations was present. The latter case occurred when no data were available or the available data did not allow any of the other 3 conclusions. In this case, the conclusion “There is no hint of (greater) benefit or (greater) harm” was drawn.

Finally, an assessment of benefit and harm across outcomes was performed.

4 Results

4.1 Results of information retrieval

The information retrieval revealed 9 relevant RCTs, all of which were already known from the previous report S19-02.

All 9 RCTs identified were relevant for research question 1. Of these, 1 RCT was relevant for research question 2. In addition to the documents known from the previous report S19-02, 2 new publications with relevant data on the LUSI and UKLS studies were identified.

In addition, 1 planned and 2 ongoing studies were identified for research question 1. Moreover, 4 studies with unclear status and 1 completed study without reported results were identified. A further 3 ongoing studies were identified for research question 2. The last search took place on 23 January 2024.

The search strategies for bibliographic databases and study registries can be found in the appendix.

Table 1: Study pool of the benefit assessment

Study	Available documents	
	Full publication (in scientific journals)	**Registry entry / results report from study registries**
Question 1 - Low-dose CT screening vs. no screening		
DANTE	yes [5-9]	yes [10] / no
DLCST	yes [11-26]	yes [27] / no
ITALY	yes [28-38]	yes [39] / no
LSS	yes [40-43]	yes [44] / no
LUSI	yes [45-50]	yes [51] / no
MILD	yes [52-59]	yes [60] / no
NELSON	yes [61-100]	yes [101] / no
NLST	yes [102-180]	yes [181] / yes [182]
UKLS	yes [183-193]	yes [194] / no
Question 2 - Variants of lung cancer screening		
MILD	yes [52-59]	yes [60] / no

4.2 Results for research question 1: Update of benefit assessment S19-02

4.2.1 Characteristics of the studies included in the assessment

Eight of the 9 included RCTs for research question 1 were already described in detail in report S19-02 and are not presented again here (DANTE, DLCST, ITALUNG, LUSI, MILD, NELSON, LSS and NLST). Although the ULKS study basically fulfilled the inclusion criteria of report S19-02,

no results were available for the final report S19-02 that could be used for the benefit assessment. Consequently, the study was not included in the S19-02 report and not described further.

The UKLS study [183-193] is a pilot study from the United Kingdom in which 4055 people were randomized. The subjects were allocated to either a one-off screening using low-dose CT or no screening. The planned follow-up period was 10 years. The study included men and women aged 50 to 75 years who had a ≥ 5 percent risk of developing lung cancer in the next 5 years, based on the Liverpool Lung Project risk model; Version 2 ($LLPv_2$). This risk was assessed by means of a questionnaire, including smoking status and years of smoking. The percentage of women in the study was 25% in the intervention group and 26% in the control group. The participation rate in screening (screening adherence) was 98% in the intervention group. The data for the intervention and control groups were collected from cancer and death registries.

4.2.2 Overview of patient-relevant outcomes from documents with new usable data

For the update, data on patient-relevant outcomes were extracted from the two newly identified documents on the LUSI and UKLS studies. Table 2 shows the corresponding overview of the available data on patient-relevant outcomes. In both studies, usable data on the outcome of mortality (all-cause mortality and lung cancer-specific mortality) and overdiagnosis were reported. For the LUSI study, the data from S19-02 were updated for these outcomes using the additionally identified document [1]. For the outcome "Consequences of incorrect screening results", usable data from the S19-02 report were already available for the LUSI study. For the outcomes of adverse events (AEs) and health-related quality of life, no data were reported in either study or the data were not usable for the benefit assessment.

Table 2: Matrix of patient-relevant outcomes from documents with new usable data (research question 1)

Study	Outcomes				
	Mortality	Morbidity			QoL
			Harm from screening		
	All-cause mortality and lung cancer-specific mortality	Adverse events	Consequences of incorrect screening results	Overdiagnosis	Health-related quality of life
Low-dose CT screening versus no screening					
LUSI	●	-	-	●	-
UKLS	●	-	-	●	-

●: Data were reported and were usable.
-: No data were reported in the newly identified publications or the data were not usable for the benefit assessment.

CT: computed tomography; QoL: quality of life

4.2.3 Assessment of the risk of bias of the results for studies with new usable data

For the UKLS study, the risk of bias of the results was classified as low across all outcomes. The outcome-specific risk of bias of the results for the outcomes of all-cause mortality, lung cancer-specific mortality and overdiagnosis was classified as low for the UKLS study.

For the LUSI study, the risk of bias was reviewed on the basis of the new document. The previous classification of a low risk of bias across outcomes and a high outcome-specific risk of bias of the results for all outcomes remains unchanged (see also S19-02 [1]).

4.2.4 Results on patient-relevant outcomes

In the following sections, the results from all 9 included studies are presented, where possible as an updated meta-analysis based on the new results and in each case in comparison with the results of the S19-02 report.

4.2.4.1 Mortality results

4.2.4.1.1 Results on all-cause mortality

For the comparison of low-dose CT screening versus no screening, the LUSI and UKLS studies reported data on all-cause mortality after a median follow-up period of 10 years and 7.3 years respectively.

Taking into account report S19-02 [1] for the outcome of all-cause mortality comparing low-dose CT screening versus no screening, data were available from 4 studies with a high (DLCST, ITALUNG, NELSON, UKLS) and 3 studies with a moderate (DANTE, LUSI, MILD) certainty of results. In addition, data from 2 studies (LSS and NLST) with a moderate certainty of results were available for the comparison of low-dose CT screening versus chest X-ray screening.

The data for the longest follow-up period was used for all studies.

The pooled estimate from 4 studies with a high certainty of results was not statistically significant (IDR: 0.93; 95% CI: [0.80; 1.09]; p = 0.251). Likewise, the joint analysis of the studies with a high and moderate certainty of results showed no statistically significant effect in favour of screening (IDR: 0.95; 95% CI: [0.89; 1.02]; p = 0.142, see Table 3). The inclusion of the two studies comparing low-dose CT screening versus chest X-ray screening in the analysis does not contradict the results comparing low-dose CT screening versus no screening.

Thus, there is no hint of a benefit or harm from lung cancer screening using low-dose CT for the outcome of all-cause mortality and no change from the assessment of report S19-02.

Subgroup analyses on all-cause mortality

Taking into account the data on all-cause mortality from report S19-02 [1] and the new data from the LUSI study and the UKLS study, an effect modification by the age of the CT devices, the size of the centres and the sex of the participants was again examined. The updated subgroup analyses showed no effect modification for all-cause mortality. Thus, there is no change compared to the assessment of report S19-02.

4.2.4.1.2 Results on lung cancer-specific mortality

For the comparison of low-dose CT screening versus no screening, the LUSI and UKLS studies reported data on lung cancer-specific mortality after a median follow-up period of 10 years and 7.3 years respectively. Taking into account the report S19-02 [1], data on the outcome of lung cancer-specific mortality for the comparison of low-dose CT screening versus no screening were available from 4 studies with a high (DLCST, ITALUNG, NELSON, UKLS) and 3 studies with a moderate (DANTE, LUSI, MILD) certainty of results. In addition, data with a moderate certainty of results from 2 studies (LSS and NLST) were available for the comparison of low-dose CT screening versus chest X-ray screening.

The data for the longest follow-up period was used for all studies.

The pooled estimate from 4 studies with a high certainty of results was statistically significant in favour of low-dose CT screening (IDR: 0.78; 95% CI: [0.64; 0.95]; p = 0.029). Likewise, the joint analysis of the studies with a high and moderate certainty of results showed a statistically significant effect in favour of screening (IDR: 0.79; 95% CI: [0.71; 0.89]; p = 0.002, see Table 3).

The inclusion of the two studies comparing low-dose CT screening versus chest X-ray screening in the analysis does not contradict the results comparing low-dose CT screening versus no screening.

In contrast, in report S19-02 the results on lung cancer-specific mortality showed no statistically significant effect for the pooled estimate from the 3 studies (DLCST, ITALUNG and NELSON) with a high certainty of results (IDR: 0.80; 95% CI: [0.60; 1.06]; p = 0.076). The joint analysis of the 6 studies with a moderate and high certainty of results showed a statistically significant difference in favour of low-dose CT screening (IDR: 0.81; 95% CI: [0.72; 0.91]; p = 0.004). Based on this result, an indication of a benefit of lung cancer screening using low-dose CT versus no screening was derived in report S19-02.

Thus, for the outcome of lung cancer-specific mortality, in contrast to report S19-02 [1], there is not an indication but proof of a benefit of lung cancer screening using low-dose CT versus no screening.

Subgroup analyses on lung cancer-specific mortality

Taking into account the data on lung cancer-specific mortality from report S19-02 [1] and the new data from the LUSI study and the UKLS study, an effect modification by the age of the CT devices, the size of the centres and the sex of the participants was again examined. The updated subgroup analyses showed no effect modification for lung cancer-specific mortality. Thus, there is no change compared to the assessment of report S19-02.

4.2.4.1.3 Summary assessment for the outcome of mortality

For all-cause mortality, there was no hint of benefit or harm from low-dose CT screening, but the results of the meta-analyses point towards a reduction in all-cause mortality. There was proof of a benefit for lung cancer-specific mortality.

The absolute effect estimate for all-cause mortality is 6 per 1000 persons (95% confidence interval [CI]: [-2; 12]); for lung cancer-specific mortality it is 5 per 1000 persons (95% CI: [3; 7]) (see Table 3). Since the respective estimates and the corresponding CIs for the absolute effect are of a similar magnitude, based on proof of a benefit for lung cancer-specific mortality, overall the data provide an indication of a benefit of lung cancer screening using low-dose CT versus no screening with regard to mortality.

Thus, the summary assessment for the outcome of mortality shows a change compared to the assessment of report S19-02, where only a hint of a benefit was determined.

4.2.4.2 Results on adverse events

No AE data were reported in any of the newly identified documents for the LUSI study and UKLS study.

Thus, there is no change for this outcome compared to the assessment of report S19-02, in which, based on the usable data on AEs from the DANTE study (with a moderate certainty of results), an hint of harm from lung cancer screening using low-dose CT versus no screening was derived for the outcome of AEs (see Table 3 and [1]).

4.2.4.3 Results on harm resulting directly and indirectly from screening, including the consequences of incorrect screening results and overdiagnosis

4.2.4.3.1 Results on the consequences of false-negative screening results

None of the newly identified documents on the LUSI study and UKLS study reported data on the consequences of false-negative screening results. No results on this outcome were available for the S19-02 report either [1].

4.2.4.3.2 Results on the consequences of false-positive screening results

None of the newly identified documents on the LUSI study and UKLS study reported data on the consequences of false-positive screening results.

Thus, there is no change for this outcome compared to the assessment of report S19-02 [1]. There, proof of harm from lung cancer screening using low-dose CT screening versus no screening was derived with regard to the consequences of false-positive screening results. (For further explanations see Table 3 and [1].)

4.2.4.3.3 Results on overdiagnosis

The UKLS study was deemed suitable for calculating overdiagnosis. While the intervention group was offered a screening strategy over a certain fixed period of time (screening phase, period 1), the control group observed in parallel did not receive a screening strategy (period 1). Both groups were followed up for a sufficient period of time after period 1 (period 2), namely 7.2 years. In addition, a high participation rate was reported for this study.

The LUSI study was already assessed as suitable in report S19-02.

Overdiagnosis in relation to the people invited for screening

For the LUSI and UKLS studies, the risk of overdiagnosis in relation to the people invited for screening is 0.8% and 0.5% respectively.

Overall, the risk of overdiagnosis was determined for all 9 included studies (DANTE, DLCST, ITALUNG, LSS, LUSI, MILD, NELSON, NLST, UKLS) in relation to all people invited for screening, taking into account report S19-02. The risk was between 0% and 2.2%, with a median of 0.7%. For further explanations see Table 3 and [1].

Overdiagnosis in relation to people diagnosed with lung cancer during the screening phase

For the LUSI study, the risk of overdiagnosis in relation to people diagnosed with lung cancer during the screening phase is 25.0%, for the UKLS study 25.7%.

Overall, taking into account report S19-02 [1] for 6 included studies (DLCST, ITALUNG, LUSI, NELSON, NLST, UKLS), the risk of overdiagnosis could be determined in relation to people diagnosed with lung cancer during the screening phase. The risk of overdiagnosis in the 6 studies was between 0% and 63.2%, with a median of 25.0%. For further explanations see Table 3 and [1].

Subgroup analysis

For the LUSI and UKLS studies, data was available separately for women and men.

Overall, taking into account report S19-02 [1] 3 studies (LUSI; NLST and UKLS) reported data on overdiagnosis separately by sex. As in report S19-02, these data do not indicate an effect modification of the risk of overdiagnosis by sex.

Summary assessment

Thus, there is no change for the outcome of overdiagnosis compared to the assessment of report S19-02. Proof was derived for harm from lung cancer screening by low-dose CT versus no screening with regard to overdiagnosis.

4.2.4.4 Results on health-related quality of life

None of the newly identified documents on the LUSI study and UKLS study reported data on health-related quality of life. For the report S19-02 [1] no data were available in the studies or the data could not be used for the benefit assessment. Thus, there is no change for the outcome of health-related quality of life compared to the assessment of report S19-02.

4.2.5 Overview and explanation of the results for all patient-relevant outcomes for weighing benefit and harm

The following table shows an overview and explanations for all patient-relevant outcomes for weighing benefit and harm of lung cancer screening using low-dose CT versus no screening (research question 1).

Table 3: Overview and explanation of the results for all patient-relevant outcomes for weighing benefit and harm (research question 1) (multi-page table)

Patient-relevant outcome	Results	Basic risk[a] per 1000 people	Risk[b] per 1000 invited screening participants	Absolute effect per 1000 invited screening participants [95% CI]	Explanation
Mortality					
All-cause mortality	IDR: 0.95; 95% CI: [0.89; 1.02]; p = 0,142	123	118	6 [-2; 13]	There is no proof that LD-CT screening reduces or increases all-cause mortality. However, the estimate and the confidence interval for the absolute effect are of a similar magnitude to those for lung cancer-specific mortality.
Lung cancer-specific mortality	IDR: 0.79; 95% CI: [0.71; 0.89]; p = 0.002	23	18	5 [3; 7]	Without LD-CT screening, 23 out of 1000 people die of lung cancer. With LD-CT screening, 18 out of 1000 people die of lung cancer. LD-CT screening prevents around 5 out of 1000 people from dying of lung cancer within around 10 years.[c]
Morbidity					
Adverse events[d]	AE after surgery: OR: 3.48; 95% CI: [1.41; 8.62]; p = 0.004	5	17	-12 [-37; -2]	Without LD-CT screening, 5 out of 1000 people suffer an AE after surgery, 2 of them suffer an AE with severity ≥ 3. With LD-CT screening, 17 out of 1000 people suffer an AE after surgery, 8 of them an AE with severity grade ≥ 3.
	AE with severity grade ≥ 3 after surgery: OR: 4.25; 95% CI: [0.92; 19.69]; p = 0.046	2	8	-6 [-36; 0]	LD-CT screening leads to an additional AE after surgery in 12 people, 6 of them with a severity grade ≥ 3.

Table 3: Overview and explanation of the results for all patient-relevant outcomes for weighing benefit and harm (research question 1) (multi-page table)

Patient-relevant outcome	**Results**	**Basic risk[a] per 1000 people**	**Risk[b] per 1000 invited screening participants**	**Absolute effect per 1000 invited screening participants [95% CI]**	**Explanation**
Consequences of false-negative screening results	No data reported	-	-	-	-
Consequences of false-positive screening results	See report S19-02 [1], Table 25	-	-	1 to 15	1-15 people out of 1000 receive invasive confirmatory diagnostics or surgery with subsequent benign findings.[e]
Overdiagnosis	Median of the point estimates of the individual studies for the risk of overdiagnosis in relation to people invited for screening: 0.7%	-	-	Median: 7	As a result of the screening, a median of 7 people out of 1000 screening participants are diagnosed with lung cancer that would not have caused any symptoms during the rest of the person's life. These people are subjected to diagnostic and therapeutic procedures that are unnecessary and sometimes high risk. The risk of overdiagnosis calculated from the individual studies in relation to the people diagnosed with lung cancer during the screening phase is a median of 25%.
QoL					
Health-related QoL	No usable data	-	-	-	-

Table 3: Overview and explanation of the results for all patient-relevant outcomes for weighing benefit and harm (research question 1) (multi-page table)

Patient-relevant outcome	Results	Basic risk[a] per 1000 people	Risk[b] per 1000 invited screening participants	Absolute effect per 1000 invited screening participants [95% CI]	Explanation
a. Median risk of the control group. b. Median risk of the intervention group. c. Mean follow-up period since randomization. d. Results of the DANTE study, which was the only study to report usable data on this outcome. e. Among all participants invited for screening, 0.1% to 0.3% (0.04%) suffered a (serious) complication after surgery for a benign finding. CT: computed tomography; IDR: incidence density ratio; CI: confidence interval; LD: low-dose; OR: odds ratio; QoL: quality of life; AE: adverse event					

4.3 Results for research question 2: Benefit assessment of variants of lung cancer screening

No new documents or studies for research question 2 could be identified from the current information retrieval. The MILD study is therefore the only RCT available to answer research question 2. As this study was already described in report S19-02 [1] for both intervention groups (annual screening and biennial screening), the characteristics will not be presented again. The results on patient-relevant outcomes with corresponding effect estimates for the comparison of biennial screening versus annual screening are presented again.

4.3.1 Characteristics of the studies included in the assessment

The MILD study has already been described in report S19-02 [1] and is not described again here.

4.3.2 Overview of patient-relevant outcomes

The following table shows the overview of the available data on patient-relevant outcomes from the MILD study for the comparison of biennial versus annual low-dose CT screening.

Table 4: Matrix of patient-relevant outcomes (research question 2)

Study	Outcomes				
	Mortality	Morbidity			QoL
			Harm from screening		
	All-cause mortality and lung cancer-specific mortality	Adverse events	Consequences of incorrect screening results	Overdiagnosis	Health-related quality of life
Biennial versus annual low-dose CT screening					
MILD	●	-	●	●	-

●: Data were reported and were usable.
- No data were reported or the data were not usable for the benefit assessment.

CT: computed tomography; QoL: quality of life

4.3.3 Evaluation of the risk of bias of the results

In the S19-02 report, the risk of bias of the results for the MILD study was classified as high across all outcomes [1]. It was unclear whether the randomization sequence was adequately generated and whether masking of group allocation was ensured. Consequently, the risk of

bias across outcomes, which was classified as high, still leads to a high outcome-specific risk of bias of the results, so that no further outcome-specific assessment was carried out for this study.

4.3.4 Results on patient-relevant outcomes

4.3.4.1 Mortality results

4.3.4.1.1 Results on all-cause mortality

For the comparison of biennial versus annual low-dose CT screening, the MILD study showed no statistically significant difference in all-cause mortality after a median follow-up period of 10 years since randomization (HR: 0.80; 95% CI: [0.57; 1.12]; p = 0.191).

Therefore, there was no hint of greater benefit or greater harm for biennial versus annual low-dose CT screening with regard to the outcome of all-cause mortality.

4.3.4.1.2 Results on lung cancer-specific mortality

For the comparison of biennial versus annual low-dose CT screening, the MILD study showed no statistically significant difference in lung cancer-specific mortality after a median follow-up period of 10 years since randomization (HR: 1.10; 95% CI: [0.59; 2.05]; p = 0.760).

Therefore, there was no hint of a greater benefit or greater harm for biennial versus annual low-dose CT screening with regard to the outcome of lung cancer-specific mortality.

4.3.4.1.3 Summary assessment for the outcome of mortality

Taking into account the results for the sub-outcomes of all-cause mortality and lung cancer-specific mortality, the summary assessment shows no hint of a greater benefit or greater harm of biennial versus annual low-dose CT screening for the outcome of mortality.

4.3.4.2 Results on adverse events

There were no usable results on AEs.

4.3.4.3 Results on harm resulting directly and indirectly from screening, including the consequences of incorrect screening results and overdiagnosis

4.3.4.3.1 Results on the consequences of false-negative screening results

Results on the consequences of false-negative screening results were not available.

4.3.4.3.2 Results on the consequences of false-positive screening results

For the outcome “consequences of false-positive screening results”, results on invasive diagnostic procedures in patients with benign findings and lung resections in patients with benign histology were extracted from the MILD study. Overall, there was no statistically

significant difference in the results for the comparison of biennial versus annual low-dose CT screening (OR: 3.02; 95% CI: [0.31; 29.03]; p = 0.332 or OR: 7.04; 95% CI: [0.36; 136.47]; p = 0.084).

Therefore, there was no hint of a greater benefit or greater harm for biennial versus annual low-dose CT screening with regard to the outcome "consequences of false-positive screening results".

4.3.4.3.3 Results on overdiagnosis

According to IQWiG methods, only studies in which no screening is offered to the control arm are suitable for quantifying the proportion of cases with overdiagnosis, as otherwise overdiagnosis may occur in both arms. In the MILD study, it was therefore not possible to calculate overdiagnosis using only the data on biennial and annual screening. However, the risk of overdiagnosis for the screening variants could still be calculated due to the control group that was monitored at the same time.

Compared to no screening, the risk of overdiagnosis in relation to people invited to screening was 0% (95% CI: [0; 1.5]) for biennial screening and 1.4% (95% CI: [0; 3.1]) for annual screening. Thus, the estimates for both screening variants were in a similar range. The comparison of the risks yielded a statistically insignificant result (risk difference [biennial vs. annual]: -1.5%; 95% CI: [-3.1; 0.1]; p-value [CSZ test] = 0.071).

Thus, there was no hint of a greater benefit or greater harm for biennial versus annual low-dose CT screening with regard to the outcome of overdiagnosis.

4.3.4.4 Results on health-related quality of life

There were no usable results on health-related quality of life.

4.4 Summary assessment of the results for research question 1 and research question 2

Evidence map

The following table shows the evidence map in relation to the patient-relevant outcomes.

Table 5: Evidence map in relation to patient-relevant outcomes (research questions 1 and 2)

Mortality	Morbidity				Health-related quality of life
All-cause mortality and lung cancer-specific mortality	Adverse events	Harm from screening			
		Consequences of false-negative screening results	Consequences of false-positive screening results	Overdiagnosis	
Question 1					
⇑[a]	⇘	-	⇓⇓	⇓⇓	-
Question 2					
⇔	-	-	⇔	⇔	-

⇓⇓: Proof of harm from low-dose CT screening
⇑: Indication of a benefit of low-dose CT screening
⇘: Hint of harm from low-dose CT screening
⇔: No hint, indication or proof
-: No (usable) data reported
a. Based on proof of a benefit for lung cancer-specific mortality and a consistent, but not statistically significant, effect on all-cause mortality.

CT: computed tomography

Weighing benefit and harm

Table 3 shows an overview of the results for the Update of benefit assessment S19-02 (question 1).

Lung cancer screening using low-dose CT is estimated to prevent 5 out of 1000 people (95% CI: [3; 7]) from dying of lung cancer within about 10 years and may extend the lifespan of some of these screened participants compared to no screening. Very few data on AEs were available for the intervention and control groups, but it can be assumed that the effect of screening on the AE rate is essentially represented by the outcome of overdiagnosis. Due to false-positive screening results, at least 1 in 1000 people, but no more than 15 in 1000 people, undergo invasive procedures that would not have been performed without screening. Overdiagnosis is to be considered as harm due to unnecessary follow-up diagnostics and treatment, including the related complications. The median risk of overdiagnosis is 7 per 1000 people invited for screening. The median risk of overdiagnosis in relation to people diagnosed with lung cancer during the screening phase is 25%. The benefit in terms of mortality is primarily offset by the harm from false-positive screening results and overdiagnosis. Overall, the benefit of low-dose CT screening outweighs harm for (former) heavy smokers.

Only one study was available for the benefit assessment of variants of lung cancer screening (research question 2). It investigated the frequency of screening (annual or biennial

screening). There was no hint of a benefit or harm of one variant over the other for any outcome. Therefore, there is no need to weigh benefit and harm.

5 Classification of the assessment result

Assessment of the scope of unpublished data

The results of 9 studies with over 94,000 people were used for the report. As already shown in report S19-02 [1] results from 3 studies are missing for which no new findings are available. 2 studies (Depiscan and Garg 2002) with a small number of cases of 400 [195] and 1000 [196] participants were published incompletely. No results were published for a further study (LUCAS) with 2000 participants, which was to investigate the feasibility, compliance and costs of a large RCT [197]. The total number of cases in these 3 studies accounts for less than 4% of the total number of cases in all included studies. A bias in the results of the report due to unpublished data is therefore unlikely. A restriction of the certainty of conclusions in the present benefit assessment is not necessary.

Update of benefit assessment S19-02

For the update of the benefit assessment of lung cancer screening using low-dose CT (S19-02), data from the UKLS study could be used in addition to the existing data from 8 RCTs. No usable data from this study were available for the final report S19-02 [1]. In addition, data with a longer follow-up period were identified for the LUSI study. The update of the analyses in S19-02 has shown that the new study data support the benefit already established. The additional results of a further study with a high certainty of results meant that the certainty of conclusions for the outcome of mortality could be upgraded.

Benefit assessment of variants of lung cancer screening

Among the possible variants of lung cancer screening using low-dose CT, only 1 study (MILD) was identified that met the inclusion and exclusion criteria of the report. This study was already known from the benefit assessment S19-02 [1]. Due to the 3-arm comparison, in which people from the intervention group received screening either annually or every 2 years and people from the control group did not receive screening, the study was relevant for both research questions. Thus, an assessment could only be made for the aspect of screening frequency and only for the variants annual or biennial screening. There was no hint that one of the two variants might have a greater benefit or harm. With regard to screening frequency, further variants are possible, such as an extension of the screening interval after a specified period or a risk-based adjustment of the screening interval.

Other variants of lung cancer screening using low-dose CT are not included in this assessment. In report S19-02, the "Considerations for the design of a screening programme" (Chapter 5 [1]) are mainly based on the framework chosen in the included studies. Aspects such as the definition of the high-risk population, smoking cessation during screening, classification and

definition of screening results, follow-up and confirmatory diagnostics after an abnormal result, as well as the types of CT devices used or software-aided diagnostic evaluation, are discussed here.

Further questions that are relevant for the implementation of lung cancer screening are currently being investigated in additional studies with a low level of evidence or other outcomes than those mentioned in this report.

As part of test accuracy studies, imaging variants, for example, are being investigated. These include computer-aided analysis and, in particular, methods based on machine learning. The use of such analysis methods is currently undergoing a much-noticed development under the collective term "artificial intelligence".

The design of smoking cessation interventions is often investigated in randomized studies. In these studies, after a study period of usually only a few months, the proportion of people who have completely stopped smoking after a smoking cessation intervention is determined. Therefore, these studies cannot be used to investigate the effects of a smoking cessation intervention on mortality. The integration of a smoking cessation intervention into lung cancer screening is considered to be very important, see A4.3.1 of the full report. The same section also contains a table of parameters that can be taken into account when designing a lung cancer screening programme.

Implementation study for the German health care context

The current HANSE study [198,199] aims to answer open questions regarding the implementation of a lung cancer screening programme in Germany.

As a randomized intervention, the study investigates whether the communication of individual risk scores (coronary calcium score, emphysema score) to the screening participants and their general practitioners represents a preventive measure to reduce cardiovascular mortality through lifestyle changes (such as smoking cessation) or cardiovascular prevention. In addition, the study could shed light on whether the definition of the high-risk group should be based on rigid criteria or whether a model-based approach should be considered. The criteria of the NELSON study, which are based solely on age and smoking history, are compared with a model-based approach (Prostate, Lung, Colorectal, and Ovarian $[PLCO]_{M2012}$ Score). This approach also takes into account body mass index, education level, ethnicity, family history of cancer and pre-existing chronic obstructive pulmonary disease (COPD) and emphysema to calculate an individual cancer risk based on an algorithm that has been previously validated in large screening cohorts. Other aspects of screening that are being investigated include the procedure for clarifying screening results and the use of biomarkers. The HANSE study is also prospectively testing the use of computer-aided analysis using

artificial intelligence as a second evaluator. A second evaluation by a radiologist is only used for intermediate cases.

6 Conclusion

Research question 1: Update of benefit assessment S19-02

For the update of report S19-02, 2 additional documents with usable data from 2 RCTs already included in report S19-02 were identified (LUSI and UKLS). Overall, results from 9 studies were thus available for the benefit assessment of screening for lung cancer using low-dose CT versus no screening.

After updating the analyses, there was still no hint of a benefit of low-dose CT screening versus no screening for overall survival.

After updating the analyses, there is proof of a benefit of low-dose CT screening for lung cancer-specific mortality. Compared with report S19-02, the certainty of the conclusions for this outcome was upgraded from an “indication” to “proof” based on the new evidence.

The results continue to support the previous assumption that screening also has a positive effect on all-cause mortality. The respective estimates and the associated confidence intervals for the absolute effect on all-cause mortality and lung cancer-specific mortality are of a similar magnitude. Considering these two mortality outcomes together therefore provides an indication of a benefit of low-dose CT screening for the outcome of mortality. Thus, overall the certainty of conclusions for this outcome was upgraded from a “hint” to an “indication” compared with report S19-02.

No new data were reported for adverse events (AEs) and consequences of incorrect screening results. Therefore, based on the analyses in report S19-02, the conclusions about the evidence for these outcomes remain unchanged: For AEs, there is a hint of harm from low-dose CT screening. For “consequences of incorrect screening results”, there is proof of harm from low-dose CT screening based on the results for consequences of false-positive screening results.

After updating the analyses, as in report S19-02, there is proof of harm from low-dose CT screening for the outcome of overdiagnosis.

As in report S19-02, there are no usable data for the outcome of health-related quality of life.

The new data from 2 studies identified in the update further substantiated the benefit of low-dose CT screening for the outcome of mortality. The proof of harm from low-dose CT screening in terms of overdiagnosis still remains after the update of the results, but this does not call into question the indication of a benefit of low-dose CT screening for mortality. In summary, the data show that there is an indication of a benefit of low-dose CT screening versus no

screening and that the benefit of low-dose CT screening outweighs harm in (former) heavy smokers. This leads to a change in the overall conclusion compared with the assessment of report S19-02. The certainty of conclusions was upgraded from a “hint” to an “indication”.

Research question 2: Benefit assessment of variants of lung cancer screening

There was only 1 study for the benefit assessment of variants of lung cancer screening. It compared screening intervals of different lengths (biennial versus annual low-dose CT screening). Therefore, the assessment of variants of low-dose CT screening was limited to the aspect of the frequency of screening and was restricted to the variants of annual and biennial screening.

For the outcomes of mortality, AEs, consequences of false-positive screening results and overdiagnosis, there was no hint of a greater benefit or greater harm from biennial versus annual low-dose CT screening. No data were available on the outcomes of consequences of false-negative screening results and health-related quality of life. In the overall assessment across outcomes, therefore no hint was derived with regard to a greater benefit or greater harm of biennial versus annual low-dose CT screening.

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Please see full rapid report for full reference list.

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The full report (German version) is published under

https://www.iqwig.de/en/projects/s23-02.html

Appendix A Search strategies

A.1 Bibliographic databases

Searches for systematic reviews

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL 1946 to November 22, 2023

The following filter was adopted:

- Systematic Review: Wong [200] – High specificity strategy
- Search lines 1 bis 13 taken from Snowsill 2018 [201]

#	Searches
1	exp Lung Neoplasms/
2	((lung$ or bronch$ or pulmon$) adj3 (cancer$ or neopla$ or tumor$ or tumour$ or carcinoma$ or adenocarcinoma$ or small cell or squamous)).ti,ab,ot,kw.
3	(NSLC or NSCLC or SLC or SCLC).ti,ab,ot,kw.
4	1 or 2 or 3
5	exp Tomography, X-Ray Computed/
6	((CT or CAT) adj3 (scan$ or screen$)).ti,ab,ot,kw.
7	((computer$ adj3 tomogra$) and (scan$ or screen$)).ti,ab,ot,kw.
8	(tomogra$ or helix or helical or spiral$ or spiro$).ti,ab,ot,kw.
9	5 or 6 or 7 or 8
10	((low$ adj3 dos$) or LDCT).ti,ab,kw,ot.
11	((ultralow$ or ultra-low$) adj3 dos$).ti,ab,kw,ot.
12	(low-dos$ or ultralow-dos$).ti,ab,kw,ot.
13	10 or 11 or 12
14	4 and 9 and 13
15	Cochrane database of systematic reviews.jn.
16	(search or MEDLINE or systematic review).tw.
17	meta analysis.pt.
18	or/15-17
19	14 and 18
20	screening*.mp.
21	4 and 9 and 18 and 20
22	19 or 21

2. International HTA Database

Search interface: INAHTA

#	Searches
1	"Lung Neoplasms"[mhe]
2	((lung* or bronch* or pulmon*) AND (cancer* or neopla* or tumor* or tumour* or carcinoma* or adenocarcinoma* or small cell or squamous))[title] OR ((lung* or bronch* or pulmon*) AND (cancer* or neopla* or tumor* or tumour* or carcinoma* or adenocarcinoma* or small cell or squamous))[abs]
3	#2 OR #1
4	"X-Ray Computed"[mhe]
5	((CT or CAT) AND (scan* or screen*))[title] OR ((CT or CAT) AND (scan* or screen*))[abs]
6	((computer* AND tomogra*) and (scan* or screen*))[title] OR ((computer* AND tomogra*) and (scan* or screen*))[abs]
7	(tomogra* or helix or helical or spiral* or spiro*)[title] OR (tomogra* or helix or helical or spiral* or spiro*)[abs]
8	#7 OR #6 OR #5 OR #4
9	((low* AND dos*) OR LDCT)[title] OR ((low* AND dos*) OR LDCT)[abs]
10	((ultralow* OR ultra-low*) AND dos*)[title] OR ((ultralow* or ultra-low*) AND dos*)[abs]
11	(low-dos* or ultralow-dos*)[title] OR (low-dos* or ultralow-dos*)[abs]
12	#11 OR #10 OR #9
13	screen*[title] OR screen*[abs]
14	#12 AND #8 AND #3
15	#13 AND #8 AND #3
16	#15 OR #14

Search for primary studies

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) 1946 to January 09, 2024

The following filter was adopted:

- RCT: Lefebvre [202] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2023 revision)

#	Searches
1	exp Lung Neoplasms/
2	(lung adj1 (cancer* or tumo?r* or neoplasm*)).ab,ti.
3	or/1-2
4	exp Tomography, X-Ray Computed/
5	(compute* adj3 tomograph*).ab,ti.
6	(ct or ldct).ab,ti.
7	or/4-6
8	Mass Screening/
9	Early Detection of Cancer/
10	screen*.mp.
11	or/8-10
12	("Nederlands-Leuvens Longkanker Screenings ONderzoek" or "Dutch-Belgian Randomized Lung Cancer Screening Trial" or NELSON or "Lung Cancer Screening Intervention trial" or LUSI or "National Lung Screening Trial" or NLST or "Lung Screening Study" or LSS or LungSearch or "Multicentric Italian Lung Detection" or MILD or "Italian Lung Cancer Screening Trial" or ITALUNG or "Danish Lung Cancer Screening Trial" or DLCST or "UK Lung Cancer Screening" or UKLS or "Detection And screening of early lung cancer with Novel imaging TEchnology" or DANTE or "4-in-the-lung-run" or "HANSE*").ab,ti,kw.
13	exp Randomized controlled Trial/
14	controlled clinical trial.pt.
15	(randomized or placebo or randomly or trial or groups).ab.
16	drug therapy.fs.
17	or/13-16
18	17 not (exp animals/ not humans.sh.)
19	and/3,7,11,18
20	and/3,11-12
21	or/19-20
22	21 and (english or german or multilingual or undetermined).lg.
23	22 and 20200601:3000.(dt).

2. Embase

Search interface: Ovid

- Embase 1974 to 2024 January 09

The following filter was adopted:

- RCT: Wong [200] – Strategy minimizing difference between sensitivity and specificity

#	Searches
1	exp Lung tumor/
2	(lung adj1 (cancer* or tumo?r* or neoplasm*)).ab,ti.
3	or/1-2
4	exp Computer assisted tomography/
5	(compute* adj3 tomograph*).ab,ti.
6	(ct or ldct).ab,ti.
7	or/4-6
8	exp Mass screening/
9	Early diagnosis/
10	screen*.mp.
11	or/8-10
12	("Nederlands-Leuvens Longkanker Screenings ONderzoek" or "Dutch-Belgian Randomized Lung Cancer Screening Trial" or NELSON or "Lung Cancer Screening Intervention trial" or LUSI or "National Lung Screening Trial" or NLST or "Lung Screening Study" or LSS or LungSearch or "Multicentric Italian Lung Detection" or MILD or "Italian Lung Cancer Screening Trial" or ITALUNG or "Danish Lung Cancer Screening Trial" or DLCST or "UK Lung Cancer Screening" or UKLS or "Detection And screening of early lung cancer with Novel imaging TEchnology" or DANTE or "4-IN-THE-LUNG-RUN" or HANSE*).ab,ti,kw.
13	(random* or double-blind*).tw.
14	placebo*.mp.
15	or/13-14
16	15 not (exp animal/ not exp human/)
17	and/3,7,11,16
18	and/3,11-12
19	or/17-18
20	19 not medline.cr.
21	20 not (Conference Abstract or Conference Review).pt.
22	21 not ((afrikaans or albanian or arabic or armenian or azerbaijani or basque or belorussian or bosnian or bulgarian or catalan or chinese or croatian or czech or danish or dutch or english or esperanto or estonian or finnish or french or gallegan or georgian or german or greek or hebrew or hindi or hungarian or icelandic or indonesian or irish gaelic or italian or japanese or korean or latvian or lithuanian or macedonian or malay or norwegian or persian or polish or polyglot or portuguese or pushto or romanian or russian or scottish gaelic or serbian or slovak or slovene or spanish or swedish or thai or turkish or ukrainian or urdu or uzbek or vietnamese) not (english or german)).lg.
23	22 and 20200601:3000.(dc).

3. The Cochrane Library

Search interface: Wiley

- Cochrane Central Register of Controlled Trials Issue 1 of 12, January 2024

#	Searches
1	[mh "Lung Neoplasms"]
2	(lung NEAR/1 (cancer* or tumor* or tumour* or neoplasm*)):ti,ab
3	#1 or #2
4	[mh "Tomography, X-Ray Computed"]
5	(compute* NEAR/3 tomograph*):ti,ab
6	(ct or ldct):ti,ab
7	#4 or #5 or #6
8	[mh ^"Mass Screening"]
9	[mh ^"Early Detection of Cancer"]
10	screen*:ti,ab,kw
11	#8 or #9 or #10
12	("Nederlands-Leuvens Longkanker Screenings ONderzoek" or "Dutch-Belgian Randomized Lung Cancer Screening Trial" or NELSON or "Lung Cancer Screening Intervention trial" or LUSI or "National Lung Screening Trial" or NLST or "Lung Screening Study" or LSS or LungSearch or "Multicentric Italian Lung Detection" or MILD or "Italian Lung Cancer Screening Trial" or ITALUNG or "Danish Lung Cancer Screening Trial" or DLCST or "UK Lung Cancer Screening" or UKLS or "Detection And screening of early lung cancer with Novel imaging TEchnology" or DANTE or "4-IN-THE-LUNG-RUN" or HANSE*):ab,ti,kw
13	#3 AND #7 AND #11
14	#3 AND #11 AND #12
15	#13 or #14
16	#15 not (*clinicaltrial*gov* or *trialsearch*who* or *clinicaltrialsregister*eu* or *anzctr*org*au* or *trialregister*nl* or *irct*ir* or *isrctn* or *controlled*trials*com* or *drks*de*):so
17	#16 not ((language next (afr or ara or aze or bos or bul or car or cat or chi or cze or dan or dut or es or est or fin or fre or gre or heb or hrv or hun or ice or ira or ita or jpn or ko or kor or lit or nor or peo or per or pol or por or pt or rom or rum or rus or slo or slv or spa or srp or swe or tha or tur or ukr or urd or uzb)) not (language near/2 (en or eng or english or ger or german or mul or unknown)))
18	#17 with Publication Year from 2020 to 2023, in Trials

A.2 Study registries

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Type of search: Basic Search

Search strategy
(lung cancer AND (computed tomography OR CT OR LDCT) AND screening)[other terms]

2. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: https://trialsearch.who.int
- Type of search: Standard Search

Search strategy
lung cancer AND (computed tomography OR CT OR LDCT)