Policy Research Unit on cancer awareness, screening and early diagnosis

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UK Lung Screening Trial

Statistical Analysis Plan

Version number: 1.0
Version date: 20/10/2020

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SAP Reference documents
ISRCTN78513845

SOP: Barts CTU GEN ST 01, V4 September 2017

Gamble et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. JAMA. 2017;318(23):2337-2343. [1]

CONSORT 2010 [2]

SPIRIT 2013 Statement [3]

UKLS publications [4, 5, 6]

Document Version History

Version Number	Version Date	Summary of changes
1.0	20/10/2020	First signed off version

Contents

1. General

1.1 SAP scope

The statistical analysis plan covers the reporting of the trial for the trial outcomes during follow up. It will be applied to the cleaned data set prepared for analysis. Analysis relating to cost-effectiveness is not covered by this document.

1.2 Abbreviations

AE	Adverse Event
CI	Confidence Interval
CT	Computed Tomography
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
IDMC	Independent Data Monitoring Committee
IMD	Index of Multiple Deprivation
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention To Treat ("Intention to screen" in the context of this trial)
LDCT	Low Dose Computed Tomography
LHC	Lung Health Check
NHS	National Health Service
NIHR	National Institute of Health Research
NLST	National Lung Screening Trial
PHE	Public Health England
RCT	Randomised Controlled Trial
RR	Relative Risk
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
UKLS	UK Lung Screening (Trial)

2. UKLS Trial Summary

UKLS is a two-arm, parallel, randomised trial of invitation to a single round of lung cancer screening with LDCT versus a no intervention control. UKLS used a Wald single-screen design. The study was conducted at two thoracic centres: Liverpool Heart and Chest Hospital, Merseyside and Papworth Hospital, Cambridgeshire. Full trial details are listed in the HTA report [5].

2.1 Randomisation Method

Eligible, consenting participants were randomised in a 1:1 manner by computer into the intervention arm (LDCT scan, screen group) or the control arm (usual care, non-screen group) and stratified by centre.

2.2 Sample Size

For a relative risk of lung cancer mortality of 0.69 after three years, based on a single screen intervention, with 90% power to detect a significant difference with 2-sided testing at the 5% level, and allowing for a compliance rate of 80%, it was determined that 16,000 participants would need to be recruited into each arm. For the pilot stage, the target recruitment total was 4,000 participants (2,000 in each arm).

2.3 Outcomes

2.3.1 Primary Outcome

- Lung cancer mortality

The primary outcome for the primary analysis is lung cancer mortality defined as death during the follow-up period where lung cancer was listed as the underlying cause of death in the UK civil registrations data provided by NHS Digital. This will be compared by trial arm in the primary analysis.

2.3.2. Secondary Outcomes

The following outcomes will be compared by trial arm:

- Incidence of lung cancer
- All-cause mortality
- Cancer mortality – this will include any cancer or metastases specified as the underlying cause of death
- Mortality from causes other than lung cancer
- Mortality from all causes in lung cancer cases only
- Mortality from causes other than lung cancer in lung cancer cases only
- Lung cancer stage
- Incidence of late stage lung cancer (diagnosed stage III or IV)
- Histological type of lung cancer

The following outcomes will be investigated in the CT intervention arm:

- Adherence to single screen, and by sex
- Adverse Events

Diagnostic work up cascade has previously been reported in the HTA report [5]

- Of those receiving a CT screen, lung cancer diagnoses by nodule classification (1-4).

2.4 Follow up

Incidence of lung cancer and mortality outcomes were obtained through cancer and death registration data supplied by NHS digital. The start date of follow up is from date of consent. The follow-up period for incidence of lung cancer and for mortality outcomes will be stated in the published report. For the initial follow up report, the follow-up period is up to 29 February 2020 for mortality and up to 31 December 2019 for incidence of lung cancer.

3. Study Data

Data sets include:

- Epidemiological baseline data from patient completed questionnaires.
- Clinically completed data uploaded to UKLS database for CT screen detected cancers.
- Follow up data from PHE and NHS Digital

These are stored on a secure network folder dedicated to the UKLS trial at the University of Liverpool. The UKLS Information Lead will collate and prepare data for analysis. The Information lead will produce a pseudonymised data set which will be encrypted and sent from the University of Liverpool to the UKLS statistician where it will be stored on a secure server in a dedicated network folder for the UKLS trial at Barts Cancer Centre, Queen Mary University of London.

4. Analysis

There were no planned interim analyses and no formal stopping rules for the UKLS pilot study. Analysis will be conducted in Stata with the version number to be reported in the published report. Statistical tests will be two-sided unless specified otherwise.

4.1 Descriptive summaries

The full CONSORT detailing the flow of patients through the study has been reported in the HTA report. For the main analysis, for the purposes of publication, the CONSORT flow diagram may be restricted from the point of numbers of eligible patients through to randomisation and follow up for primary analysis.

Baseline data will be presented descriptively by trial arm and in total for all randomised participants. Length of follow up will be reported with median and inter-quartile range. Numbers of lung cancers and lung cancer deaths will be reported alongside cumulative person-years of follow-up.

4.2 Primary analysis of primary outcome

4.2.1 Lung cancer mortality

The primary outcome is lung cancer mortality. For the primary analysis lung cancer death is defined as death where the underlying cause of death according to civil registration data is lung cancer (see primary outcome above).

Primary analysis will be conducted on an intention to screen basis, including participants in the groups to which they had been randomised. Cumulative lung cancer mortality over time will be compared by trial arm using Poisson regression. Relative risk will be presented with 95% CIs and associated p-value. The primary analysis will be verified by a second statistician.

Cumulative hazard plots will be produced using the Nelson-Aalen method.

If fewer than 90% of those invited to a screen did not attend a screen, then a secondary per-protocol analysis will performed whereby those allocated to the screening arm who did not undergo CT screening will be excluded.

4.3 Analyses of secondary outcomes

Cumulative lung cancer incidence and other secondary mortality outcomes over time (all-cause mortality, cancer mortality, mortality from causes other than lung cancer, mortality from all causes in lung cancer cases only, mortality from causes other than lung cancer in lung cancer cases only) and incidence of late stage disease will be compared by trial arm using Poisson regression. Relative risks will be presented with 95% CIs and associated p-values. Cumulative hazard plots will be produced using the Nelson-Aalen method.

Stage distribution and histological type will be compared by trial arm by Pearson's chi-squared test.

4.4 Sensitivity Analyses

None planned unless imbalance is found in comparison of important baseline factors in which case analyses will be repeated using a model adjusted by the factor with imbalance.

4.5 Subgroup Analysis

4.5.1 Sex (Male, Female)

The following outcomes will be investigated by sex:

- Lung cancer mortality
- Lung cancer incidence
- All-cause mortality in those diagnosed with lung cancer
- Lung cancer stage

4.6 Missing data

Primary and secondary outcomes are collected through national cancer and death registration data via NHS digital. This means potential sources of missing data could include type 1 and type 2 objectors, individuals who have not had true lung cancer diagnoses or deaths identified and recorded. Lung cancer incidence will be checked for imbalance between trial arms. Lung cancer stage and histological data may be unknown or missing for lung cancer cases and this will be reported clearly in the relevant tables. No extra formal analyses will be carried to check for missing data.

5. Meta-analysis Plan

The primary research question for the meta-analysis planned here is "Does a policy of invitation to LDCT screening reduce lung cancer mortality in adults at enhanced risk?". The meta-analysis will include the most recent evidence from randomised controlled trials, including results from the UKLS study outlined in this SAP. This will provide an updated meta-analysis of randomised evidence in this field and allow the UKLS results to be reported in context of the wider evidence.

5.1 PICO and outcomes

Population: Adults aged >49 who are at enhanced risk
Intervention: Invitation to LDCT screening
Comparator: No invitation to LDCT screening
Primary **O**utcome: Lung cancer mortality
Secondary outcome: all-cause mortality

5.2 Collating and reviewing the randomised evidence

There are three comprehensive meta-analyses known to the investigators *a priori* that have been published in this field since 2019 (Sadate et al [7], Huang et al [8], Hoffman et al [9]). All randomised trials found in these studies will be considered for inclusion in this meta-analysis together with the results of the UKLS trial. In addition, a literature search will be carried out based on search strategies published by Snowsill et al [10] and Huang et al [8] using the OVID interface to find relevant publications since 01 January 2019 on the Medline database to check for new/updated trial publications for additional inclusion. The date of the search will be reported. The search terms are given below in Table 1. The strategy has been checked for sensitivity in terms of finding the relevant trial publications included in the previous systematic reviews when applied to publications since 2015.

Two reviewers will check the title and abstracts of the search results for relevance, with a third reviewer consulted should there be disagreement on relevance for inclusion (see 5.2.1 Eligibility criteria below).

For relevant studies, data will be extracted into pre-defined tables and data required for analysis will be stored in Stata. Extracted data will at least include: study name, year started, reference details including first author and date published, countries, number randomised, eligibility criteria (age-range, high-risk criteria), screening type, comparator type, screening rounds and intervals, follow-up, and outcome measures.

Quality assessment on studies included will be conducted using the Cochrane risk of bias tool (RoB 2) [11].

Table 1: Search strategy

Line	Search Term
1	Lung Neoplasms/
2	"lung neoplasm*".ab,ti.
3	1 or 2
4	((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.
5	(NSLC or NSCLC or SLC or SCLC).ti,ab,ot,kw.
6	Tomography, X-Ray Computed/
7	((CT or CAT) adj3 (scan* or screen*)).ti,ab,ot,kw.
8	((computer* adj3 tomogra*) and (scan* or screen*)).ti,ab,ot,kw.
9	(tomogra* or helix or helical or spiral* or spiro*).ti,ab,ot,kw.
10	((low* adj3 dos*) or LDCT).ti,ab,ot,kw.
11	((ultralow* or ultra-low*) adj3 dos*).ti,ab,ot,kw.
12	(low-dos* or ultralow-dos*).ti,ab,ot,kw.
13	randomized controlled trial.pt.
14	controlled clinical trial.pt.
15	randomized.ti,ab.
16	randomly.ti,ab.
17	trial.ti,ab.
18	13 or 14 or 15 or 16 or 17
19	3 or 4 or 5
20	6 or 7 or 8 or 9
21	10 or 11 or 12
22	19 and 20 and 21 and 18
23	limit 22 to yr="2019 -Current"
24	exp Animals/ not humans.sh.
25	23 not 24

5.2.1 Eligibility criteria for meta-analysis

Studies with all the following characteristics will be included:

- Randomised trials of LDCT screening for lung cancer
- Non-LDCT control arm
- High-risk population of adults aged >49 years
- Measure lung cancer mortality with at least a median of 3 years of FU

5.3 Meta-analyses

Meta-analysis will be carried out using the “metan” suite of commands in Stata.

5.3.1 Primary meta-analysis

The meta-analysis will combine data to produce a summary risk ratio for lung cancer mortality and 95% confidence intervals assuming a random effects model using the DerSimonian & Laird method, with the estimate of heterogeneity being taken from the Mantel-Haenszel model. Statistical heterogeneity will be reported using the Chi^2 test and I^2 statistic, whereby a reported p value<0.05 would indicate significant heterogeneity and I^2 values of 30–60%, 50–90%, and 75–100% are considered to indicate moderate, substantial and considerable heterogeneity.

Sources of substantial heterogeneity will be investigated in terms of specific study results and subgroup analyses excluding sources of heterogeneity may be reported.

5.3.2 Secondary meta-analyses

The meta-analysis method described above will be repeated for the outcome of all-cause mortality

5.3.2 Subgroup analysis

Analyses for the outcome of lung cancer mortality will be repeated sex (males, females).

6.0 References

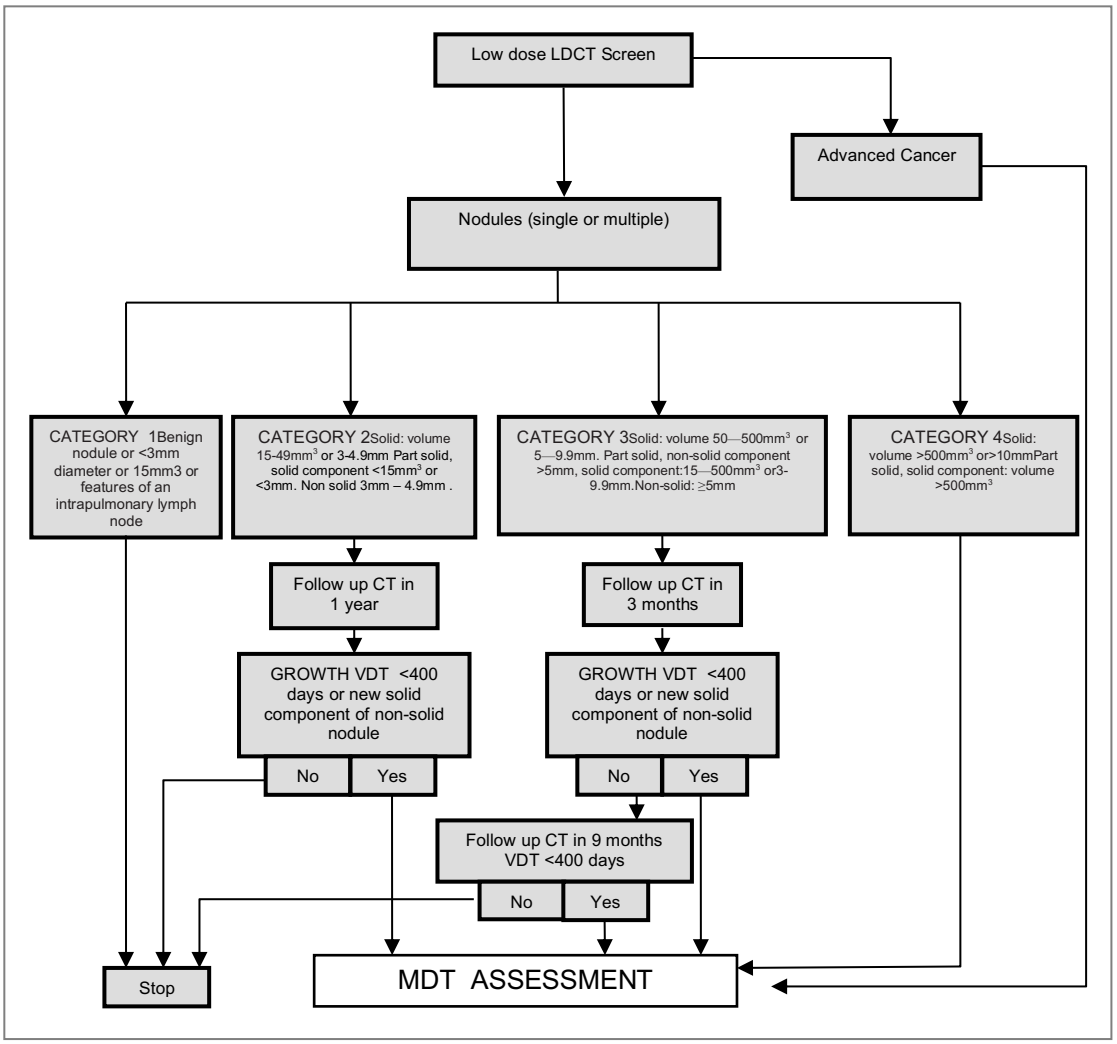
1. Gamble C, Krishan A, Stocken D, et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. *JAMA* 2017; **318**(23): 2337-43.
2. Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *Trials* 2010; **11**: 32.
3. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013; **158**(3): 200-7.
4. Baldwin DR, Duffy SW, Wald NJ, Page R, Hansell DM, Field JK. UK Lung Screen (UKLS) nodule management protocol: modelling of a single screen randomised controlled trial of low-dose CT screening for lung cancer. *Thorax* 2011; **66**(4): 308-13.
5. Field JK, Duffy SW, Baldwin DR, et al. The UK Lung Cancer Screening Trial: a pilot randomised controlled trial of low-dose computed tomography screening for the early detection of lung cancer. *Health Technol Assess* 2016; **20**(40): 1-146.
6. Field JK, Duffy SW, Baldwin DR, et al. UK Lung Cancer RCT Pilot Screening Trial: baseline findings from the screening arm provide evidence for the potential implementation of lung cancer screening. *Thorax* 2016; **71**(2): 161-70.
7. Sadate A, Occean BV, Beregi JP, et al. Systematic review and meta-analysis on the impact of lung cancer screening by low-dose computed tomography. *Eur J Cancer* 2020; **134**: 107-14.
8. Huang KL, Wang SY, Lu WC, Chang YH, Su J, Lu YT. Effects of low-dose computed tomography on lung cancer screening: a systematic review, meta-analysis, and trial sequential analysis. *BMC Pulm Med* 2019; **19**(1): 126.
9. Hoffman RM, Atallah RP, Struble RD, Badgett RG. Lung Cancer Screening with Low-Dose CT: a Meta-Analysis. *J Gen Intern Med* 2020.
10. Snowsill T, Yang H, Griffin E, et al. Low-dose computed tomography for lung cancer screening in high-risk populations: a systematic review and economic evaluation. *Health Technol Assess* 2018; **22**(69): 1-276.
11. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; **366**: l4898.

7.0 Signatures of Approval

The sign-off relates to the SAP version 1.0, dated 20/10/2020

Name	Role	Signature	Date
John Field	Chief Investigator		20/10/2020
Michael Davies	Information Lead		20/10/2020
Stephen Duffy	Lead Statistician		20/10/2020
Daniel Vulkan	Trial Statistician		20/10/2020
Rhian Gabe	Senior Statistician		20/10/2020

Figure S1 UKLS Nodule Care Pathway Management Protocol



Category 1:Benign nodules fulfilling one of the following criteria: a benign pattern of calcification, presence of fat, nodules measuring <3mm in diameter or volume <15mm^3. Or: Intrapulmonary lymph nodes fulfilling the following criteria: they lie within 5 mm of the pleura, are <8mm in diameter, are smooth bordered and ovoid and have at least one interlobular septum or linear opacity radiating from their surface.

Category 2: If solid and intraparenchymal, volume of 15-49mm^3 or maximum diameter of 3-4·9mm, if nodules could not be segmented by volumetry software. If solid and pleural or juxtapleural, a maximum diameter of 3-4·9mm. If non-solid or part solid, a maximum diameter of the ground glass component of 3-4·9 mm. If part-solid, the solid component has a diameter of <3mm and/or volume of <15mm^3.

***Category 3*:** If solid and intraparenchymal, a volume of 50-500mm^3 or diameter of 5-9·9mm if nodules could not be segmented by volumetry software. If solid and pleural or juxtapleural, a diameter 5-9·9mm. If non-solid or part-solid, a diameter of the ground-glass component of >5mm. If part solid, the solid component has a volume of 15-500 mm^3 or has a maximum diameter of 5–9·9 mm.

***Category 4*:** If solid and intraparenchymal, a volume >500mm3 or ≥100mm if nodules could not be segmented by volumetry software. If solid and pleural or juxtapleural, a diameter of ≥10 mm. If part solid, the solid component has a diameter of ≥10mm or has a volume >500mm^3

Nodules were managed as follows:

No nodules or Category 1 nodules: No further action required.

Category 2 nodules: Follow up CT scan at 12 months.

Category 3 nodules: Follow up CT scan at 3 months and (if required) subsequently 12 months from baseline.

Category 4 nodules: Referral to Multidisciplinary Team (MDT).

Where follow up scans (at 3 or 12 months) were performed, the volume doubling time (VDT) of the nodule was calculated. VDTs were designated as: < 400 days or ≥400 days.

Table S1

Lung cancer incidence and mortality by sex

	Screen arm	Control arm	Total
Males	1495	1473	2968
Lung cancers	62 (4.1%)	57 (3.9%)	119 (4.0%)
Lung cancer deaths	22 (1.5%)	34 (2.3%)	56 (1.9%)
Females	492	508	1000
Lung cancers	24 (4.9%)	18 (3.5%)	42 (4.2%)
Lung cancer deaths	8 (1.6%)	12 (2.4%)	20 (2.0%)
Total	1987	1981	3968
Lung cancers	86 (4.3%)	75 (3.8%)	161 (4.1%)
Lung cancer deaths	30 (1.5%)	46 (2.3%)	76 (1.9%)

Supplementary LDCT Meta-analysis Tables and Figures

Table 1: Literature search strategy

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to November 02, 2020>		
Date of Search: 03 Nov 2020		
Line	**Search Term**	**Hits**
1	Lung Neoplasms/	(220276)
2	"lung neoplasm*".ab,ti.	(1061)
3	1 or 2	(220503)
4	((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.	(241051)
5	(NSLC or NSCLC or SLC or SCLC).ti,ab,ot,kw.	(52848)
6	Tomography, X-Ray Computed/	(383586)
7	((CT or CAT) adj3 (scan* or screen*)).ti,ab,ot,kw.	(106537)
8	((computer* adj3 tomogra*) and (scan* or screen*)).ti,ab,ot,kw.	(12167)
9	(tomogra* or helix or helical or spiral* or spiro*).ti,ab,ot,kw.	(614980)
10	((low* adj3 dos*) or LDCT).ti,ab,ot,kw.	(187206)
11	((ultralow* or ultra-low*) adj3 dos*).ti,ab,ot,kw.	(1169)
12	(low-dos* or ultralow-dos*).ti,ab,ot,kw.	(130316)
13	randomized controlled trial.pt.	(516213)
14	controlled clinical trial.pt.	(93908)
15	randomized.ti,ab.	(537977)
16	randomly.ti,ab.	(344775)
17	trial.ti,ab.	(613271)
18	13 or 14 or 15 or 16 or 17	(1359774)
19	3 or 4 or 5	(314357)
20	6 or 7 or 8 or 9	(882522)
21	10 or 11 or 12	(187686)
22	19 and 20 and 21 and 18	(720)
23	limit 22 to yr="2019 -Current"	(154)
24	exp Animals/ not humans.sh.	(4751699)
25	23 not 24	(154)

Figure 1: Flow diagram of search

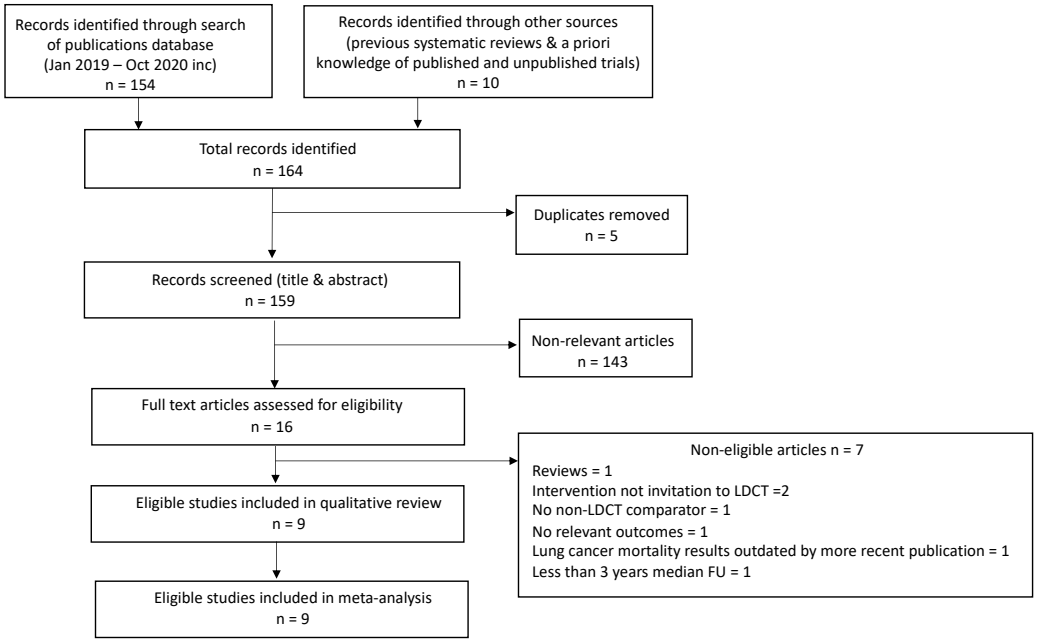


Table2: Excluded studies

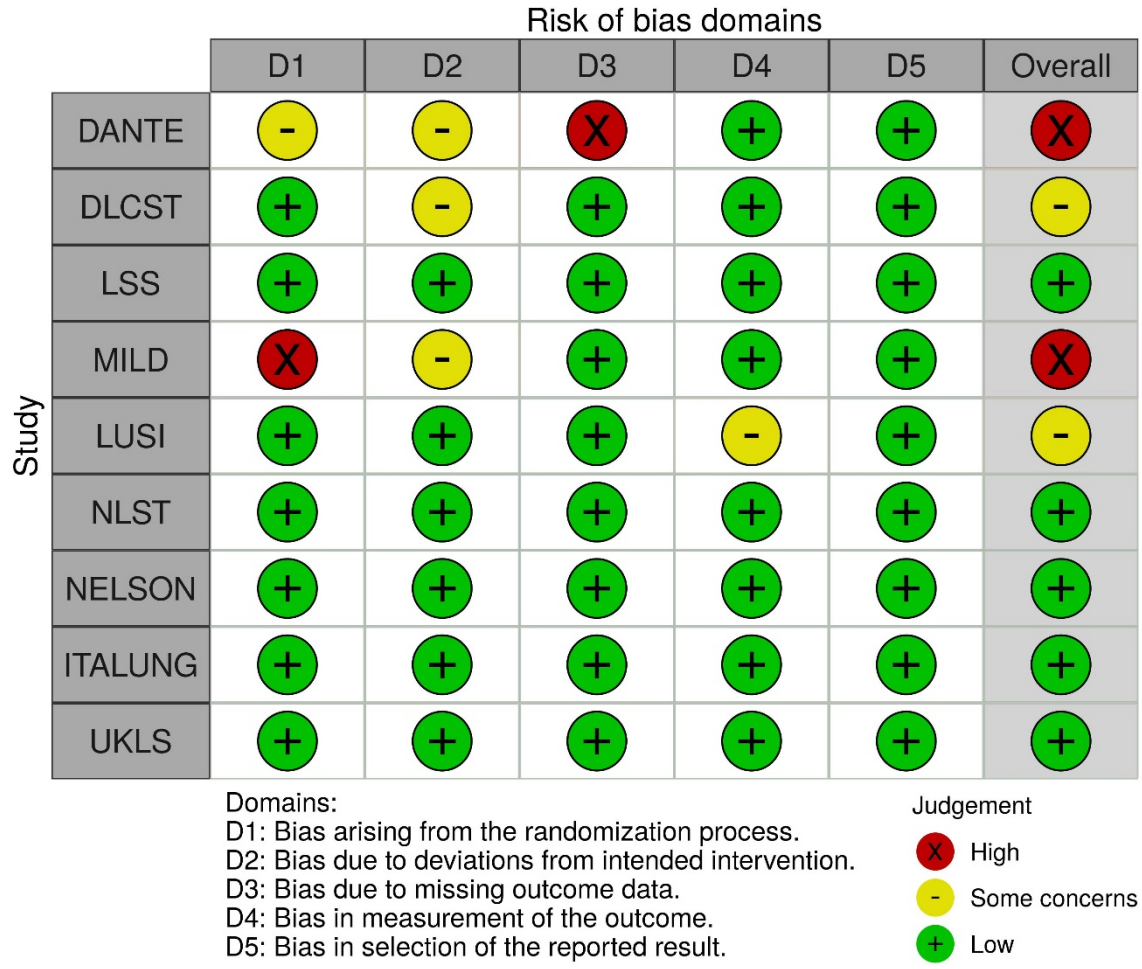
	Reference	Reason Excluded
1	Tang X, Qu G, Wang L, Wu W, Sun Y. Low-dose CT screening can reduce cancer mortality: A meta-analysis. Revista Da Associacao Medica Brasileira. 65(12):1508-1514, 2019	Review
2	Sullivan et al. Earlier diagnosis of lung cancer in a randomised trial of an autoantibody blood test followed by imaging. Eur Respir J 2020	Intervention not invitation to LDCT
3	Spiro et al. Sequential screening for lung cancer in a high-risk group: randomised controlled trial: LungSEARCH: a randomised controlled trial of Surveillance using sputum and imaging for the EARly detection of lung Cancer in a High-risk group. European Respiratory Journal. 54(4), 2019.	Intervention not invitation to LDCT
4	Pastorino et al. Ten-year results of the Multicentric Italian Lung Detection trial demonstrate the safety and efficacy of biennial lung cancer screening. European Journal of Cancer. 118:142-148, 2019.	No non-LDCT comparator
5	Gonzalez Maldonado et al. Overdiagnosis in lung cancer screening: Estimates from the German Lung Cancer Screening Intervention Trial. International Journal of Cancer 2020	No relevant outcomes
6	Paci et al. Mortality, survival and incidence rates in the ITALUNG randomised lung cancer screening trial. Thorax 2017;72:825–831.	Lung cancer mortality results outdated by more recent publication*
7	Yang et al. Community-based lung cancer screening with low-dose CT in China: Results of the baseline screening. Lung Cancer 2018	Less than 3 years median FU

Table 3: Study characteristics of RCTs of LDCT screening for lung cancer included (ordered by year of most recent publication)

Trial	Year started	Reference/s (1st author, year)	Countries	Comparator	Number randomised	Age range (years)	Risk criteria	Screening rounds	Intervals between screens (years)	Median FU (years)
UKLS	2011	Field, 2020	UK	No screening	4055	50-75	$LLP_{v2} \geq 4.5\%$ risk over 5 years	1	N/A	7
NELSON	2003	de Koning, 2020	Netherlands Belgium	No screening	15,822	50-75	≥15 cigarettes/day for ≥25 years, or ≥10 cigarettes/day for ≥30 years	4	1, 2, 2.5	10
NLST	2002	NLST Research Team, 2019	USA	CXR*	53,454	55-74	≥30 pack-years	3	1,1	12.3
LUSI	2007	Becker, 2019	Germany	No screening	4052	50-69	≥15 cigarettes/day for ≥25 years, or ≥10 cigarettes/day for ≥30 years	5	1, 1, 1, 1	8.8
MILD**	2005	Pastorino, 2019	Italy	No screening	4099	>49	≥20 pack-years	10 5	1, 1, 1, 1, 1, 1, 1 ,1 ,1 2, 2, 2, 2	10
LSS	2000	Doroudi, 2018	USA	CXR	3318	55-74	≥30 pack-years	2	1	5.2
ITALUNG	2004	Paci, 2020 Paci, 2020	Italy	No screening	3206	55-59	≥20 pack-years	4	1, 1, 1	9.3 11.3
DLCST	2004	Wille, 2016	Demark	No screening	4104	50-70	≥20 pack-years	5	1, 1, 1, 1	9.8
DANTE***	2001	Infante, 2015	Italy	Baseline CXR***	2811	60-74	≥20 pack-years	5	1, 1, 1, 1	8.35

*NLST controls invited to 3 annual CXR = Chest X-ray. **MILD has two intervention arms: annual and biennial screening. ***DANTE, both LDCT and Control arms had baseline CXR, so test addition of LDCT screening to baseline CXR.

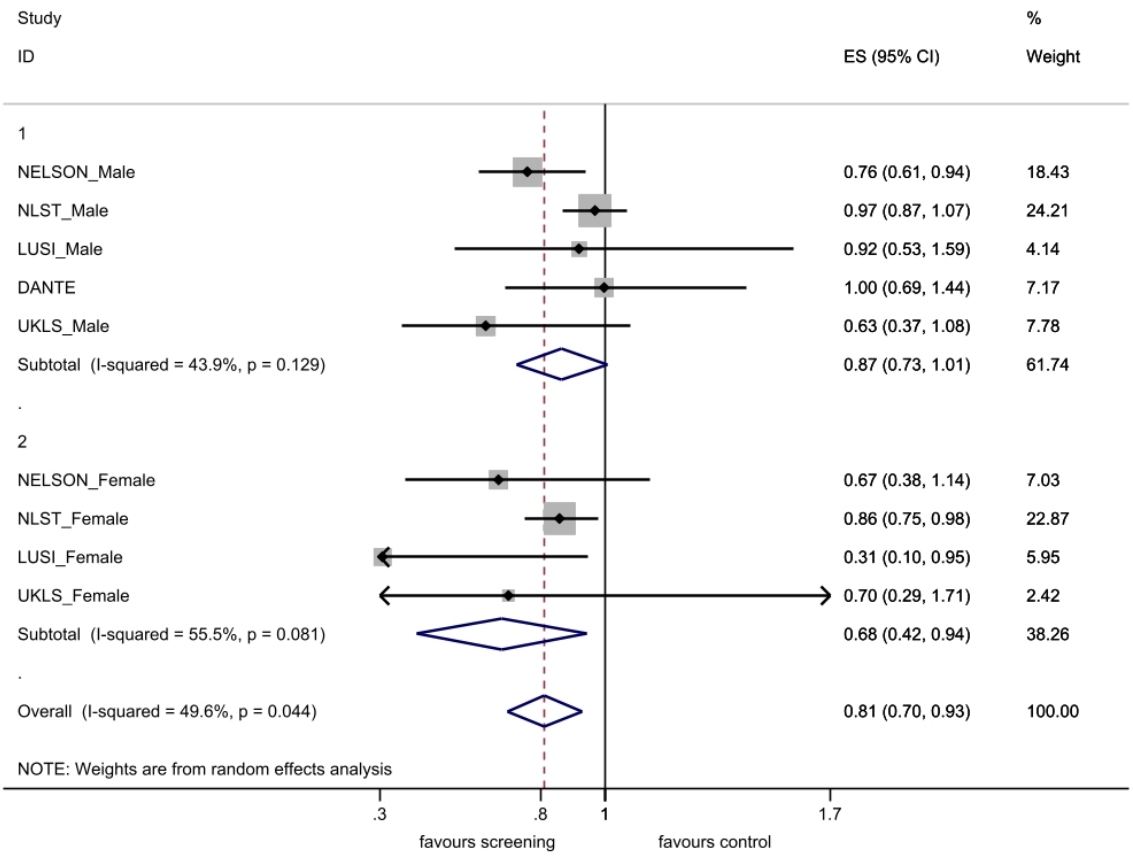
Fig 2: Risk of Bias



Citation for use of the Robvis tool: McGuinness, LA, Higgins, JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. Res Syn Meth. 2020; 1- 7. https://doi.org/10.1002/jrsm.1411

Created online from: https://mcguinlu.shinyapps.io/robvis/

Figure 3: Forest Plot: Lung Cancer Mortality by Sex



Significance test for difference by subgroups, indicates p=0.27 (not significant)