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Low-dose CT screening for lung cancer

Scope

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Abbreviations

ALCA	Anti-Lung Cancer Association
AUD	Australien Dollar
BIA	Budget impact analysis
CAD	Canadian Dollar
CEA	Cost-effectiveness analysis
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	Confidence interval
CT	Computed tomography
CUA	Cost-utility analysis
CXR	Chest X-ray
ELCAP	Early Lung Cancer Action Project
EUR	Euro
GBP	Great Britain Pound
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HPFS	Health Professionals Follow-up Study
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
ICTRP	International Clinical Trial Registry Platform
JPY	Japanese Yen
IV	Inverse-variance
LDCT	Low-dose computed tomography
Lung-RADS	Lung Imaging Reporting and Data System
LUSI	Lung tumor screening and intervention trial
LYG	Life-year gained
M-H	Mantel-Haenszel method
MISCAN	MIcrosimulation Screening ANalysis-Lung
NHS	UK National Health Services
NHS EED	Economic Evaluation Database from the UK National Health Service
NLST	US National Lung Screening Trial
NIHR	UK National Institute for Health Research
OIS	Optimal information size
PanCan	Pan-Canadian Early Detection of Lung Cancer
PICO	Population, intervention, comparator and outcomes
PLCO	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
RR	Relative risk
SD	Standard deviation
SEER	Surveillance Epidemiology and End Results
SMD	Standardized mean difference
UKLS	UK Lung Cancer Screening Trial
USD	United States Dollar
WHO	World Health Organization

1 Background

Each year, lung cancer is responsible for 1.6 to 1.8 Mio death worldwide[1,2] and for about 3200 death in Switzerland.[3] Over 20% of cancer-related death in Switzerland are caused by lung cancer.[3] Lung cancer growth remains usually undetected until later cancer stages compromising treatment options and success. Five-year survival in patients with advanced cancer stages is around 5%, whereas for early stages the five-year survival is up to 50%.[4] Screening for lung cancer in a high-risk population has therefore the potential to shift the detection to earlier cancer stages and treatment and to reduce cancer related mortality. There is evidence from one large randomized US National Lung Screening Trial (NLST, >53,000 participants randomized), demonstrating that screening with low-dose computed tomography (LDCT) compared to chest radiograph reduces lung cancer mortality. Ten-years follow-up results of the second largest lung cancer screening trial NELSON (>15,000 participants randomized) indicate an important reduction in lung cancer mortality with LDCT compared to no screening. At least seven smaller trials, but still with several thousand participants, have investigated the comparative effectiveness of LDCT versus no screening. Lung cancer screening programs using LDCT have been established in the US, UK and Poland. Several countries, including Switzerland, have not yet implemented such population-based programs as several questions like the burden for the work of positive or suspicious CT scans and costs of follow-up procedures in a real-world setting remain insufficiently addressed. For example, the NLST trial reported that a quarter of all LDCT scans were positive, thereof 96.4% were false-positives scans.[5]

2 Aims of the Health Technology Assessment report

The aims of the HTA report are

- to systematically assess the clinical effectiveness (benefit and harm) of lung cancer screening with LDCT compared to no screening or any other screening method relevant for the Swiss setting
- to assess the cost-effectiveness and potential budget impact of LDCT screening programs for lung cancer
- to address the ethical issues raised by LDCT screening.

3 Clinical effectiveness

3.1 Existing literature

A systematic search for evidence syntheses was conducted on January 20, 2020, in MEDLINE via Pubmed and the Cochrane library. The search strategy consisted of terms related to lung cancer and were combined with terms related to screening and LDCT. A total of 125 hits were screened. Thereof, 51 hits were published before 2014, including the only Cochrane review which was published in 2013, and were checked for their relevance, but will not be further considered in the present scope. Of the 74 hits published in 2014 or later, 56 were not relevant (no systematic evidence syntheses n=18, wrong population n=23, wrong intervention n=11, health economic analyses n=2, protocol n=1 and Chinese language n=1). Of the remaining 18 relevant evidence syntheses, seven included only randomized controlled trials (RCTs) (Section 3.1.1) and 11 also included non-randomized trials (Section 3.1.2).

3.1.1 Evidence syntheses on randomized controlled trials

The most recent Cochrane review[6] on LDCT lung cancer screening was published in 2013. Trials comparing LDCT with no screening were still ongoing at this time point and no data on mortality was published. The most recent and high-quality evidence synthesis is the Health Technology Assessment report published in 2018 commissioned by the UK National Institute for Health Research (NIHR).[7] The findings of this report were partly published in a peer-reviewed journal.[8] The NIHR report provides a comprehensive overview of eight partly published and one ongoing randomized trials comparing LDCT with no screening.[7] However, data on mortality was available for only three trials[9, 10 11] as the systematic literature search was conducted in January 2017. The pooled effect for lung cancer mortality of these three trials was not statistically significant (relative risk [RR] 1.15, 95% CI 0.79 to 1.67). A recently published systematic review Huang 2019[12] on LDCT lung cancer screening pooled lung cancer mortality data of seven trials and reported a RR of 0.78 (95% CI 0.68 to 0.89, I^2=0%) in favor of the LDCT when compared to no screening. The potential reduction of lung cancer mortality is still subject to uncertainty because Huang 2019 pooled preliminary results of two RCTs (Yang 2018[13] and NELSON[14]). Moreover, Huang 2019 did not analyze the potential harm from lung cancer screening due to diagnostic work-up and over-diagnosis. Six other evidence syntheses on RCTs were identified, two systematic reviews[15,16] reported findings (including relevant RCTs) which were largely overlapping with the Huang 2019 or the NIHR report, and two systematic reviews were outdated.[17,18]

3.1.2 Evidence syntheses also including non-randomized studies

Three recent evidence syntheses have considered randomized and non-randomized controlled trials.[19-21] Interestingly, the number of participants from RCTs outnumbers the one from participants in non-randomized trials and so, most of the available evidence on harm derives from randomized controlled trials. For example, Usman 2016 concluded that a invasive procedures were part of follow-up investigations in 403 participants with benign conditions from the total of 40,569 participants, of whom 36,000 did participate in RCTs.[20] Several available RCTs have a fairly large sample size of several thousand participants, whereas two RCTs form the largest body of evidence in term of participants, the NLST from the US and the NELSON trial from the Netherlands.

Several evidence syntheses assessed endpoints which were not relevant for the present scope: One systematic review assessed demographic differences in screening programs[22], one assessed only the early cancer detection rates[23], two assessed how lung cancer screening influenced smoking behaviour[24,25] and two investigated psychological burden of lung cancer screening.[26,27]

Two systematic reviews[28,29] evaluated lung cancer screening in an asbestos-exposed population. No RCTs were included. In the included cohorts, the number of events (mortality) were mostly very low or not reported, and long-term follow-up results were rare.

3.1.3 NLST - The National Lung Cancer Screening Trial

The National Lung Cancer Screening Trial randomized 53,454 participants with high risk for lung cancer to either LDCT (n=26,722) or chest radiography (n=26,732) in 33 US medical centers. Compared to chest radiography screening, LDCT screening reduced lung cancer mortality by 20% (relative risk reduction: 20%, 95% CI 6.8 to 26.7).[5,30] Because of its high internal validity and the large cohort size, NLST is considered as strongest evidence for the benefit of lung cancer screening. However, the beneficial effect on lung cancer mortality is accompanied by a considerable false-positive rate of 96.4% in the LDCT and 94.5% in the chest radiography group. The consequences of false-positive scans are expressed in absolute numbers for the LDCT group: 18,146 of all 75,126 CT scans over three screening rounds were positive. Of all positive scans 17,497 were false-positive, and most of them were subjected to follow-up investigations. Over 39% of the participants in the LDCT group had at least one positive scan during the three screening rounds. In the NLST trial, all non-calcified nodules with larger diameter of 4 mm were considered as positive scan, this relatively unspecific definition was probably the main driver for the high false-positive rates.

Importantly, the generalizability of the NLST for the Swiss setting is considered to be limited. First, Swiss institutions follow guidelines with a more complex definition for positive scans (e.g. following the Fleischner Society Guidelines[31]), which results in substantial fewer false-positive results (see also below the definition of positive scans in the NELSON trial). Second, chest radiography is not recommended, mainly because no health benefit has been demonstrated from routine chest radiography screening in smoking individuals.[32] Hence, NLST lacks a relevant comparator (e.g. no screening). Despite of these two important limitations for the Swiss setting, a network meta-analysis for the outcomes lung cancer mortality and all-cause mortality between LDCT, chest X-ray and no screening will be performed.

3.1.4 NELSON - Dutch-Belgian lung cancer screening trial

The Dutch-Belgian lung cancer screening trial (NELSON) is the largest trial comparing LDCT screening to no screening. NELSON randomized 7915 smokers (or former smokers) to LDCT screening and 7155 to no screening.[33] NELSON was completed in 2018 and the recently published 10 years follow-up data showed that LDCT screening compared to no screening reduces lung cancer mortality in males (cumulative rate ration: 0.76, 95% CI 0.61 to 0.94).[34] The screening, however, did not affect the all-cause mortality. The NELSON trial reported a false-positive scans rate of 56%[33,34], and hence, much lower than in the NLST. In absolute numbers, 467 (2.1%) of the 22,600 scans during three screening rounds were positive scans, thereof, 264 were false-positive scans. In the NELSON trial, the definition of a positive scan was based on the volume of the nodule or its growth rate. Scans were classified into negative, positive or indeterminate. Indeterminate scans required follow-up LDCT and were then classified into positive or negative scan based on lesion volume doubling time.[35]

3.1.5 Ongoing trials

The Clinicaltrials.gov register was systematically searched for ongoing RCTs on December 4, 2019. Ninety-one trials were screened, and three ongoing trials were identified, one Canadian and two Chinese trials (Table 1). The one Chinese trial (NCT03975504) is a follow-up trial of the other Chinese trial (NCT02898441).

Table 1: Ongoing trials

Clinicaltrials.gov Country	Planned start Completion date	N participants to be enrolled	Published results
NCT02431962[36] **Canada**	April, 2015 December 2019	800 at risk	Only on smoking cessation rates[37]
NCT02898441[38] **China**	January 1, 2014 December 2018	6000 participants with high-risk for lung cancer	Screening observation after first round, mortality rates for 2 year follow-up[13]
NCT03975504[39] **China**	August 1, 2018 July 31, 2023	6000 high-risk subjects	No

3.2 Aim

The assessment of the clinical effectiveness aims to summarize the highest available evidence to inform health policy decision-makers about the potential benefit and harm of lung cancer screening with LDCT in smokers and former smokers compared to no screening.

In addition to the direct comparison of LDCT screening with no screening, a network meta-analysis will be performed taking into account RCTs comparing LDCT screening with chest X-ray (e.g. NLST) and RCTs comparing chest X-ray with no screening. This "triangular" network of three screening strategies will be limited to the outcomes lung cancer mortality and all-cause mortality. Details for the network meta-analysis are described in Section 3.3.9.

3.3 Methods

3.3.1 Overview of the eligibility criteria

The overview of eligibility criteria (PICO-Question) used in the literature selection process is shown in Table 2.

Table 2: PICO-Question for the assessment of clinical effectiveness

PICO-Question	
Population	Smokers and former smokers (see section 3.3.2.1)
Intervention	Low-dose computed tomography (see section 3.3.2.2)
Comparator	No screening/ usual care and chest X-ray (see section 3.3.2.3)
Outcomes	Critical and important patient-relevant outcomes (see section 3.3.2.4)
Study design	Randomized and quasi-randomized controlled trials (see section 3.3.2.5)
Languages	English, German, French (see section 3.3.2.6)

3.3.2 Eligibility criteria

3.3.2.1 Population

Any asymptomatic adult population (≥18 years) at high risk of lung cancer due to smoking will be eligible.

3.3.2.2 Interventions

Any screening with LDCT irrespective of the number of screening rounds or screening intervals.

3.3.2.3 Comparators

No screening or usual care or chest X-ray. Screening with chest X-ray will be considered for two outcomes in a network meta-analysis (see section 3.3.9).

3.3.2.4 Outcomes

Critical outcomes:

- Lung cancer mortality (at least 5 years follow-up)
- All-cause mortality (at least 5 years follow-up)
- Number of false-positive scans with invasive procedures (e.g. fine-needle biopsy, bronchoscopy or surgery) --> A false-positive scan is defined as a positive scan result (leading to further testing or treatment) when lung cancer was absent. As the definitions of false-positive scans might vary between trials, the definition of false-positive scans will be extracted for each trial.
- Number of false-positive scans with complications --> A false-positive scan is defined as a positive scan result (leading to further testing or treatment) when lung cancer was absent. As the definitions of false-positive scans might vary between trials, the definition of false-positive scans will be extracted for each trial. As the definitions for complications might vary between trials, the definition for complications following invasive and non-invasive diagnostic procdures will be extracted for each trial.

Important outcomes:

- Number of false-positive scans --> A false-positive scan is defined as a positive scan result (leading to further testing or treatment) when lung cancer was absent. As the definitions of false-positive scans might vary between trials, the definition of false-positive scans will be extracted for each trial.
- Number of indeterminate scans --> A indeterminate scan is defined as a scan which does no allow to classify the lung cancer as being present or absent. Indeterminate scans result in further testing. As the definitions of indeterminate scans might vary between trials, the definition of false-positive scans will be extracted for each trial.
- Number of follow-up assessment with LDCT
- Number of lung cancer detected
- Lung cancer stage --> not patient-relevant, however, early detection requires less severe therapeutic measures
- Interval lung cancer detection (after negative-screening result or undetermined-screening result without follow-up CT scan)

- Psychological distress (depression, anxiety, stress, other)
- Overdiagnosis
- Smoking cessation rate
- Number and type of lung cancer treatment
- Number of follow-up investigations (invasive and non-invasive)
- Quality of life

Further parameters or outcomes may be added during the assessment, especially if they are relevant to inform the health economic evaluation.

3.3.2.5 Study design

Relevant study designs will include randomized controlled trials (RCT) and quasi-RCTs (with assignment of treatment based on, e.g., alteration or date of birth). Although the latter methods for randomization are deemed inadequate, these study types will be considered because it can be assumed that individuals in such studies were prospectively assigned to the intervention or the comparator.[40]

3.3.2.6 Languages

Trials published in English, French, and German will be eligible for inclusion.

3.3.3 Literature search

The literature search will comprise Medline ALL and EMBASE via OvidSP, CINAHL ("Cumulative Index to Nursing and Allied Health Literature") via EBSCO and CENTRAL ("Cochrane central register of controlled trials"). In addition, reference lists of systematic reviews will be screened for trials that fulfill the inclusion criteria.

The topic-specific search strategy will be combined with a search filter for randomized controlled trials (RCTs). The search strategy will not be restricted by adding terms for the comparator. Conference proceedings or conference booklets will not be searched.

Two reviewers will independently screen titles/abstracts of records found in the literature search for potentially eligible studies after removal of duplicate publications. Subsequently, two reviewers independently will screen the full-text articles of the potentially eligible studies in order to identify eligible RCTs. Discrepant screening results will be discussed and will be resolved by consensus or by third-party arbitration. Protocols of included RCTs will be searched for within the US trial registry (clinicaltrials.gov) and WHO trial registry.

The US trial registry (clinicaltrials.gov) and WHO trial registry (International Clinical Trial Registry Platform, ICTRP) will be searched for unpublished or still ongoing trials.

3.3.4 Data extraction

Data on study characteristics and patient-relevant outcomes will be extracted into a standardized form by one reviewer and checked by another. Discrepancies will be resolved by discussion or third-party arbitration.

Information on patient recruitment time, maximum follow-up time, setting and country, eligibility criteria, and description of the screening interventions (including information accompanying smoking cessation programs) will be extracted. General study population characteristics (age, sex, smoking behavior/status, etc.) and characteristics of the lung cancer-positive population (cancer stage, histologic type, etc.) will be extracted. Radiation exposure will not be extracted, but will be discussed in the HTA report and existing literature on radiation exposure will be referenced.

Outcome data will be extracted for the latest follow-up time-point. However, earlier time-points will be extracted if drop-out rates for the later follow-up time-point are high (>30%) or unbalanced between arm (>5%).

Continuous outcome data will be extracted as mean values for each intervention group at follow-up or, if not reported, as mean change from baseline.

For binary outcomes, the number of patients experiencing an event will be extracted and analyzed, and not the number of events themselves. If only the number of events will be available, this information will be extracted and will be summarized in the relevant sections. Pooling of number of events will only be considered if consistently reported by all trials.

For missing information, study authors will be not contacted.

3.3.5 Risk of bias and quality of evidence assessment

One reviewer will assess the internal validity (risk of bias assessment) of each trial. This will be checked by a second reviewer. Discrepancies will be resolved by discussion or third-party arbitration.

To assess the risk of bias of individual trials the following criteria will be used[40-56]:

- adequate random sequence generation (selection bias)
- adequate concealment of treatment allocation (selection bias)
- adequate blinding of patients and healthcare providers (performance bias)
- adequate blinding of outcome assessors (detection bias)
- complete outcome data (attrition bias)
- reporting bias

Risk of bias for each of the aforementioned criteria will be assessed as low, high or unclear in each trial. It will be taken into consideration that blinding of outcome assessors is of less relevance for some outcomes (e.g. overall mortality) than for patient-reported outcomes. To judge the completeness of outcome data and the resulting risk of attrition bias, the following operationalization will be used:

- The risk of attrition bias will be judged low if the proportion of patients with missing data is 0 - 10% in either study arm and comparable between the randomized treatment arms.
- The risk of attrition bias will also be judged low if the proportion of patients with missing data is between 10-20% per arm, is comparable between the randomized treatment arms, and is being addressed using adequate methods. In case of continuous data, methods considered to be adequate are multiple imputation methods but not simple replacement methods like “last observation carried forward” or “baseline value carried forward”. In case of binary data adequate methods to address missing data are conservative assumptions about missing data; i.e. those patients with missing data in the control arm are treated in the analysis as if they had had beneficial outcome results.
- Missing data in the treatment arms will be considered comparable if the difference between the intervention and control group are 5% or less.
- The risk of attrition bias will be judged high if more than 20% of the data were missing irrespective of how the missing data were addressed in the analysis.

Reporting bias will be judged low if all outcomes (relevant for the present review) described in the trial protocol (or trial registry) are reported in the results section of the publication. If the trial was not registered or no trial protocol is available, reporting bias will be judged unclear.

The quality of the evidence will be judged by one reviewer and checked by another according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) on the outcome level by considering all the available trials for the respective outcome. Discrepancies will be resolved by consensus or third-party arbitration. The following criteria will be considered to judge the quality of the evidence[41-56]:

Criteria for rating down the quality of evidence:

- risk of bias (internal validity)
- inconsistency
- indirectness
- imprecision
- publication bias

Criteria for rating up the quality of evidence:

- large magnitude of effect
- dose-response gradient
- all plausible confounders or other biases increase the confidence in the estimated effect

Imprecision refers to the confidence in the effect estimate. For continuous outcomes, the precision will be adequate if the optimal information size (OIS) is sufficient (simple sample size calculation to estimate whether the total number of included patients would be sufficient for an adequately powered RCT) and for binary outcomes, if the number of events is sufficient (rule of thumb >300 events).[47] If the sample size or number of events is sufficiently large, the 95% CI of the effect estimate will be examined. If the 95% CI is narrow enough not to include both the "no effect" line and a possible clinically relevant effect (also called minimal clinically important difference) precision will be judged as adequate.[47]

Using the GRADEpro GDT software[57] results of the judgment will be presented in a summary of findings table.

3.3.6 Data synthesis

Study characteristics and results of the eligible trials will be presented per study in tables and will be descriptively summarised.

Where possible, outcome results will be summarised quantitatively in a meta-analysis by using a random-effects model. Therefore, the inverse-variance (IV) method[58] for continuous outcomes and the Mantel-Haenszel method[40] (M-H) for binary outcomes will be applied.

Continuous outcomes will be presented as mean differences. For binary outcomes, relative risks (RR) will be determined. Effect estimates (summary and single for each trial) with the corresponding 95% confidence interval will be presented in forest plots.

If a continuous outcome is measured on different scales, mean differences of the individual trial results will be standardized using the following formula:

Standardized mean difference (SMD) = $(\text{mean}_{\text{intervention}} - \text{mean}_{\text{comparator}})/\text{SD}_{\text{pooled}}$

An effect size above 0.2 SDs will be considered to correspond to a small effect; effect sizes above 0.5 SDs to a medium effect and above 0.8 SDs will be considered to correspond to large effects[59,60].

Heterogeneity of pooled effect estimates will be estimated using I^2. Estimates of I^2 will be interpreted under the guidance of the Cochrane Handbook[40]. Heterogeneity with an I^2 of 0% to 40% will be considered low, 41% to 60% will be considered moderate, and 61% to 100% will be considered high. The interpretation of the observed I^2 value will depend on other measures for heterogeneity, namely Tau^2 (a Tau^2 value of 0.04, 0.09, and 0.16 represent low, moderate and high heterogeneity, respectively), the precision of the individual effect estimates of the included RCTs, and visual examination.[40,61]

In case of substantial or considerable heterogeneity, methodological and clinical factors that might explain the heterogeneity will be explored in subgroup and sensitivity analyses.

3.3.7 Subgroup analyses

To assess possible variations of treatment effects the following subgroup analyses will be considered:

- Internal validity (trial of high vs. low internal validity)
- Population characteristics (age groups, sex, number of cigarette package years)
- Population at risk (e.g. patient with smoking history vs. exposure to asbestos vs. family history of lung cancer)
- LDCT screening (single vs. multiple screening)
- Different definitions for positive CT scans (e.g. based on diameter of non-calcified nodules vs. definitions based on volume and volume-doubling time).

The sequence of the subgroup analyses listed above corresponds to the sequence in which the subgroup analyses will be performed depending on the available evidence.

Subgroup differences will be assessed by interaction tests available within Review Manager 5.3 and according to the Cochrane Handbook.[40]

3.3.8 Sensitivity analyses

In case of substantial or considerable heterogeneity (high I^2), and if too few RCTs are available for subgroup analysis, explorative sensitivity analyses will be conducted. Sensitivity analyses might explain how specific parameters (e.g. population or screening characteristics) might cause heterogeneity. Further criteria for sensitivity analyses might be defined a posteriori and will strictly labeled as such.

3.3.9 Network meta-analysis

A network meta-analysis will be performed in addition to the direct comparison of LDCT screening with no screening. The random-effects network meta-analysis will be performed for two outcomes lung cancer mortality and all-cause mortality, and consists of three connected nodes (LDCT, chest X-ray and usual care/no screening) (Figure 1). Based on the data availability, either a Bayesian or frequestist random-effects method will be used. Through the use of this network meta-analysis external evidence from trials comparing chest X-ray with no screening can be borrowed to assess the comparative effectiveness of no screening with LDCT and to compare the effectiveness of chest X-ray with LDCT. The relative effects of the compared screening strategies will be reported as RRs with corresponding credibility intervals.[62-64] Statistical analysis will be performed using an R package "gemtc". The confidenence in the results of the network meta-analysis will be assessed with CINeMA.[65]

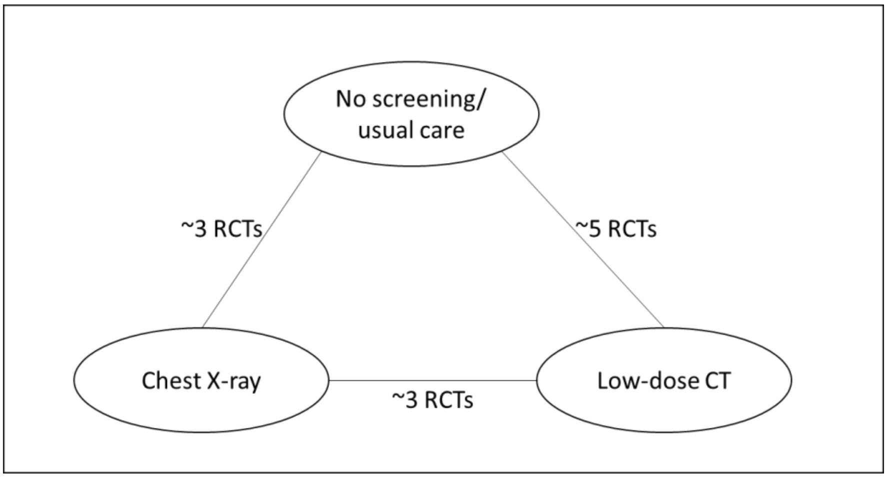

Figure 1 Network map of the network meta-analysis

4 Health economic evaluation

Treatment for late-stage lung cancer is rarely curative and expensive. Screening people at high risk of lung cancer before symptomatic cancer develops may help to treat them more effectively. The costs related to a screening program, including the consultation, the diagnostic, and the treatment costs (also related to false-positive results and adverse events) may be considerably high, especially if the prevalence of subjects at high risk is elevated. Investigating the cost-effectiveness and budget impact of different screening options (e.g. subject inclusion criteria, screening intensity) is therefore fundamental to identify the screening scenarios with the best balance between benefits, harms, and costs.

4.1 Aim

The health economic assessment aims to investigate the cost-effectiveness and the potential budget impact of LDCT screening programs for lung cancer in high-risk populations (i.e. smokers and ex-smokers) in Switzerland.

4.2 Pre-review of the health economic literature

As part of the scoping process, a preliminary search for health economic literature was conducted in PubMed (MEDLINE) to gain a first understanding of potentially relevant cost-effectiveness studies on lung cancer screening (e.g. cost-effectiveness, cost-utility, or cost studies). The following search strings were combined:

- Lung cancer (n=336,415)
- Screening (n=4,647,558)
- LDCT OR low-dose CT OR low-dose computed tomography OR CT OR computed tomography (n=769,110)
- Afford$ OR Budget$ OR Capital expenditure$ OR cost$ OR cost-benefit OR Cost-consequence$ OR Cost-effectiveness OR Cost-minimization OR Cost-utility OR Economic$ OR Economic evaluation OR Expenditure$ OR Fee$ OR Finance$ OR Financial OR Financing OR Health expenditure$ OR Health resource allocation OR Health resource utilization OR Health economic$ OR Medical savings accounts OR Monetary OR Pharmaco-economic analyses OR Pharmaco-economic analysis OR Pharmacoeconomic$ OR Pharmacoeconomic analyses OR Pharmacoeconomic analysis OR Price$ OR Socioeconomic$ (n=1,569,412)

The search conducted on 18 December 2019 resulted in 1,240 hits. A first title/abstract screen led to the identification of 39 potentially relevant articles published between 2001 and 2019. Among them, there were four HTAs, 30 cost-effectiveness or cost-utility analyses, three systematic reviews, and two narrative reviews.

After full-text review, ten articles were excluded for following reasons:

- Outdated Swedish HTA (published in 2003, i.e. before most of the trials on this topic were published)[66]

- Non-systematic reviews (CADTH 2015, Lew 2019)[66,67]
- Outdated systematic reviews (Puggina 2016, Raymakers 2016)[68,69]
- Systematic review in Chinese (Liu 2019)[70]
- Wrong intervention/comparators (Allen 2019, Hinde 2018, Kumar 2018)[71-73]
- Unclear population (i.e. no information on smoking behaviour of selected patients) (Kanarkievitz 2015)[74]

4.3 Brief overview of the identified cost-effectiveness analyses

The characteristics of the identified articles are summarized in Table 3.

Two-thirds of the identified articles were included in the most recent HTA conducted by Snowsill et al. on behalf of the National Institute for Health Research (NIHR) in the UK.[7] Snowsill et al. did not include a Canadian HTA published in 2014 and another eight studies published between 2017 and 2018.

All cost-effectiveness analyses included high risk population for lung cancer (mainly using the NLST inclusion criteria). The interventions ranged from one single LDCT screen to annual, biennial, or triennial screens from patient inclusion until 80 years of age. The reported comparator was no screening. However, it is important to remark that many recent publications used the results of the chest X-ray control arm of the NLST as comparator, assuming that chest X-ray is equivalent to no screening by assuming that annual screening with chest radiograph does not reduce lung cancer mortality compared with usual care.[75] While this assumption might hold for the endpoint of overall mortality this might not be true for other endpoints and in particular in regard to costs for work-up of false positive x-ray results.

The main results of the identified articles are summarized in Table 4. Similar to HTA report by Snowsill et al., the existing economic evaluations of LDCT screening for lung cancer have produced markedly variable estimates of the cost-effectiveness of screening.[7] The identified studies, using different methodological approaches as well as different effectiveness sources, reported incremental cost-effectiveness ratios (ICERs) for LDCT screening ranging from few thousands of USD to more than USD 100,000 per quality-adjusted life year (QALY) gained. Assuming a cost-effectiveness threshold of USD 100,000 per QALY, most of the identified cost-effectiveness analyses would suggest that LDCT is cost-effective if compared to no screening.

Among the identified study, one was investigating the cost-effectiveness of LDCT screening for lung cancer in Switzerland.[76] This study adapted the MIcrosimulation Screening ANalysis-Lung (MISCAN) model and used Swiss-specific input parameters for lung cancer epidemiology, smoking behaviour, and treatment costs. The model parameters for the effectiveness of CT screening were calibrated to individual-level data from the NLST. The study concluded that several LDCT screening strategies may be cost-effective in Switzerland (i.e. would show an incremental cost-effectiveness ratio below EUR 50,000 per life-year gained).

Table 3: Characteristics of the identified articles

Study author and publication year	Type of evaluation	Location, price year and currency	Population	Intervention(s)	Comparator(s)	Methodology
HTA Ontario 2014	HTA (CUA)	Alberta, 2012 CAD	NLST cohort (aged 55–74 years with ≥ 30 pack-year smoking history)	Annual and biennial LDCT screening	No screening	Microsimulation model
HTA Field 2016 #	HTA (CEA and CUA)	UK, 2011–12 GBP	Adults aged 50–75 years	Risk prediction followed by single LDCT screen	No screening	Decision tree model
HTA Snowsill 2018 [7]	HTA	UK, 2016 GBP	Adult smokers (current or former) aged 55–80	Single, triple, annual, or biennial LDCT screen	No screening	Decision tree model
Black 2014 #	CEA and CUA	USA, 2009 USD	NLST cohort (aged 55–74 years with ≥ 30 pack-year smoking history)	Annual LDCT for 3 years, Annual CXR for 3 years	No screening	Decision tree model
Black 2015 #	CEA and CUA	USA, 2009 USD	NLST cohort (aged 55–74 years with ≥ 30 pack-year smoking history)	Annual LDCT for 3 years, Annual CXR for 3 years	No screening	Decision tree model
Chirikos 2003 #	CEA	USA, 2000 USD	Adult smokers aged 45–74 years	Annual LDCT for 5 years	No screening	Cohort model
Cressmann 2017	CUA	Canada, 2015 CAD	NLST cohort (aged 55–74 years with ≥ 30 pack-year smoking history)	Annual LDCT screening	CXR (assumed to be equal to no screening)	Decision tree model
Criss 2019	CEA	USA, 2018 USD	Current, former, and never-smokers aged 45 years from the 1960 U.S. birth cohort	Annual LDCT according to NLST, CMS, and USPSTF criteria.	No screening	Microsimulation models
Goffin 2015 #	CUA	Canada, 2008 CAD	Smokers aged 55–74 years with ≥ 30 pack-year history	Annual LDCT for 3 years with smoking cessation	No intervention	Microsimulation model
Goffin 2016 #	CUA	Canada, 2008 CAD	Smokers aged 55–74 years with ≥ 30 pack-year history	Biennial LDCT screening for 20 years with/without smoking cessation	Annual LDCT screening for 20 years with/without smoking cessation	Microsimulation model

Goulart 2012 #	CEA	USA, 2011 USD	Those eligible for NLST, i.e. smokers aged 55 to 74 years	LDCT screening (frequency unclear)	No screening	Decision tree model
Hofer 2018	CUA	Germany, 2016 EUR	Ever smokers aged 55–75 with ≥ 20 cigarettes per day	Annual LDCT screening	No screening	Markov model
Jaine 2018	CUA	New Zeland, 2011 USD	NLST cohort (aged 55–74 years with ≥ 30 pack-year smoking history)	Biennial LDCT screening	CXR (assumed to be equal to no screening)	Microsimulation model
Mahadevia 2003 #	CEA	USA, 2001 USD	60-year-old heavy smokers (current and former, > 20 pack	Annual LDCT to age 80 years-years)	No screening	Markov model
Manser 2004 #	CEA and CUA	Australia, 2002 AUD	Male current smokers aged 60–64 years	Annual LDCT for 5 years	No screening	Markov model
Marshall 2001 #	CEA	USA, 1999 USD	General smokers aged 60–74 years	Single LDCT screen	No screening	Decision tree model
McMahon 2011 #	CUA	USA, 2006 USD	Current and former smokers ≥20 pack-years smoking history	Annual LDCT screening	No intervention	Patient-level microsimulation model
Pyenson 2012 #	CEA	USA, 2012 USD	Current and former smokers aged 50 years with ≥ 30 pack-year smoking history	Annual LDCT from age 50–64 years	No screening	Cohort model
Pyenson 2014 #	CEA	USA, 2014 USD	Adults aged 55–80 years with ≥ 30 pack-year smoking history	Annual LDCT from age 50–64 years	No screening	Cohort model
Shmueli 2013 #	CUA	Israel, 2011 USD	Adults aged ≥45 years with ≥10 pack-year smoking history	Single LDCT screen	No screening	Decision tree model
Tabata 2014 #	CEA	Japan, JPY (price year unclear)	Smokers aged 55–74 years	Annual LDCT	Annual CXR	Decision tree model
Ten Haaf 2017 #	CEA	Canada, 2015 CAD	Adult smokers (current or former) aged 46–75	Eligibility criteria and annual or biennial LDCT screening	No screening	Microsimulation model
Tomonaga 2018	CEA	Switzerland, 2015 EUR	Adult smokers (current or former) aged 50–80	Eligibility criteria and annual, biennial, or triennial LDCT screening	No screening	Microsimulation model
Treskova 2017	CEA	Germany, EUR (price	Smokers aged 55–74 years with ≥ 30 pack-year history	Annual LDCT for 5 years	No screening	Microsimulation model

		year unclear)				
Villanti 2013 [#]	CUA	USA, 2012 USD	Adults aged 50-64 years with ≥ 30 pack-year history	Annual LDCT screening to age 64 years	No screening	Cohort model
Wade 2018	CEA and CUA	Australia, 2015 AUD	Smokers aged 55–74 years with ≥ 30 pack-year history	Annual LDCT for 3 years	CXR (assumed to be equal to no screening)	Markov model (not clearly stated)
Whynes 2008 [#]	CUA	UK, 2004 GBP	Men aged 61 years at high risk	Single LDCT screen	No screening	Decision tree model
Wisnivesky 2003 [#]	CUA	USA, 2000 USD	Adults aged ≥60 years with ≥10 pack-year smoking history	Single LDCT screen	No screening	Decision tree model
Yang 2017	CUA	Taiwan, 2013 USD	NLST cohort (aged 55–74 years with ≥ 30 pack-year smoking history)	Annual LDCT for 3 years	No screening	Markov model (not clearly stated)

[#] Study included in the HTA published by Snowsill et al. in 2018.
CEA: cost-effectiveness analysis; CUA: cost-utility analysis; CXR: chest x-ray; HTA: health technology assessment; LDCT: low-dose computed tomography

Table 4: Main results of the identifies studies

Study author and publication year	Source of effectiveness	Health outcomes	Time horizon and discount rate	Main results
HTA Ontario 2014	NLST	QALYs	Lifetime, 3%	LDCT screening more costly and more effective than no screening, ICER CAD 92,025/QALY (annual) or CAD 67,396 (biennial)
HTA Field 2016 [#]	UKLS and estimates of lead time	Life-years, QALYs	Lifetime, 3.5%	LDCT screening more costly and more effective than no screening, ICER GBP 8,466/QALY
HTA Snowsill 2018 [7]	Natural history model calibrated to UKLS and NLST	QALYs	Lifetime, 3.5%	LDCT screening more costly and more effective than no screening, ICER GBP 28,169-40,034/QALY
Black 2014 [#]	NLST (assume same outcomes for no screening as CXR)	Life-years, QALYs	Lifetime, 3%	LDCT screening more costly and more effective than CXR and no screening, ICER (vs. no screening) USD 81,000/QALY. CXR dominated by no screening
Black 2015 [#]				
Chirikos 2003 [#]	Hypothetical stage shift	Life-years	15 years, 7.5%	LDCT more expensive and more effective than no screening, ICER USD 33,557–90,022/LYG depending on achieved stage distribution
Cressmann 2017	NLST and PanCan	QALYs	Lifetime, 3%	LDCT screening more costly and more effective than no screening, ICER CAD 20,724/QALY
Criss 2019	NHS/HPFS, SEER, NLST, PLCO, Lung-RADS	Life-years, QALYs	45 years, 3%	LDCT screening more costly and more effective than no screening, ICER USD 36,000-51,900/LYG or USD 49,200-96,700/QALY
Goffin 2015 [#]	Natural history model, partially calibrated to NLST	QALYs	20 years (lifetime), 3%	LDCT screening more costly and more effective than CXR. ICER of triple screen (vs. no screening) CAD 74,000/QALY. ICER of annual screening (vs. no screening) CAD 52,000/QALY. ICER of annual screening vs. triple screen CAD 21,000/QALY (triple screening extendedly dominated)
Goffin 2016 [#]	Natural history model partially calibrated to NLST	QALYs	Lifetime, 3%	Biennial LDCT screening cheaper and less effective than annual LDCT screening ICER of annual vs. biennial ranged from CAD 54,000 to CAD 4.8M/QALY

Goulart 2012 #	NLST	Lung cancer deaths	Unclear (possibly 1 year), no discounting	LDCT more expensive and more effective than no screening, ICER USD 240,000 per lung cancer death avoided
Hofer 2018	NLST, German LUSI trial	Life-years, QALYs	15 years, 3%	LDCT screening more costly and more effective than no screening, ICER EUR 19,302/LYG or EUR 30,291/QALY
Jaine 2018	NLST	QALYs	Lifetime, 3%	LDCT more expensive and more effective than no screening, ICER USD 104,000/QALY
Mahadevia 2003 #	Hypothetical stage shift	QALYs	40 years (to age 100), 3%	LDCT more expensive and more effective than no screening, ICER USD 116,300/QALY
Manser 2004 #	Diagnostic performance of LDCT based on 'weighted averages of six studies'	Life-years, QALYs	15 years, 3%	LDCT more expensive and more effective than no screening, ICER AUD 57,325/LYG or AUD 105,090/QALY
Marshall 2001 #	ELCAP	Life-years	5 years, 3%	LDCT more expensive and more effective than no screening, ICER USD 23,100/LYG. In 'very high-risk' cohort, ICER USD 5,940/LYG
McMahon 2011 #	Natural history model calibrated to tumour registry data and validated against screening studies	QALYs	Lifetime, 3%	LDCT more expensive and more effective than no screening. ICERs for screening consistently above USD100,000/QALY unless positive impact on smoking cessation included
Pyenson 2012 #	ELCAP	Life-years	15 years, no discounting	LDCT more expensive and more effective than no screening, ICER USD 18,862/LYG
Pyenson 2014 #	ELCAP	Life-years	20 years, no discounting	LDCT screening more costly and more effective than no screening, ICER USD 18,452/LYG
Shmueli 2013 #	Single-centre Israeli cohort study	QALYs	Lifetime, 3%	LDCT more expensive and more effective than no screening, ICER USD 1,464/QALY
Tabata 2014 #	ALCA, Japanese case–control study	Life-years	Unclear	LDCT screening more costly and more effective than CXR, ICERs ranging from JPY 983,000 to JPY 1,942,000/LYG depending on sex and age
Ten Haaf 2017 #	Natural history model calibrated to NLST	Life-years	Lifetime, 3%	576 screening scenarios evaluated. LDCT screening more expensive and more effective than no screening. 11 screening scenarios and no screening on the efficient frontier. At CAD 50,000/LYG threshold, it is cost-effective to screen annually in 55- to

				75-year-olds with ≥ 40 pack-year smoking history (quit ≤ 10 years ago if former smoker), ICER CAD41,136/LYG
Tomonaga 2018	Natural history model calibrated to NLST	Life-years	Lifetime, 3%	576 screening scenarios evaluated. LDCT screening more expensive and more effective than no screening. On the efficient frontier 15 of 27 scenarios showed an ICER < EUR 50,000 per LYG.
Treskova 2017	Natural history model calibrated to tumour registry data and validated against screening studies	Life-years	Lifetime, 3%	LDCT screening more costly and more effective than no screening, ICER EUR 16,754-23,847/LYG
Villanti 2013 [#]	ELCAP and NLST	QALYs	15 years, no discounting	LDCT more expensive and more effective than no screening, ICER USD 28,240/QALY (ELCAP) or USD47,115/QALY (NLST). Adding smoking cessation nearly doubled QALY gain from screening alone and had lower ICER
Wade 2018	NLST	Life-years, QALYs	10 years, 5% discount	LDCT more expensive and more effective than no screening, ICER AUD 138,000/LYG or AUD 233,000/QALY
Whynes 2008 [#]	ELCAP	QALYs	Unclear (perhaps 40 years), 3.5%	LDCT more expensive and more effective than no screening, ICER GBP 13,910/QALY (for men)
Wisnivesky 2003 [#]	ELCAP	Life-years	Unclear, 3%	LDCT more expensive and more effective than no screening, ICER USD 2,500/LYG
Yang 2017	NLST		Lifetime, 3%	LDCT more expensive and more effective than no screening, ICER USD 19,683/QALY

[#] Study included in the HTA published by Snowsill et al. in 2018.

ALCA: Anti-Lung Cancer Association; AUD: Australian dollar; CAD: Canadian Dollar; ELCAP: Early Lung Cancer Action Project; EUR: Euro; GBP: Great Britain Pound; HPFS: Health Professionals Follow-Up Study; HTA: health technology assessment; ICER: incremental cost-effectiveness ratio; JPY: Japanese Yen; LDCT: low-dose computed tomography; Lung-RADS: Lung Imaging Reporting and Data System; LYG: Life-year gained; NHS: National Health Service; NLST: National Lung Screening Trial; PanCan: Pan-Canadian Early Detection of Lung Cancer; PLCO: Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; QALY: quality-adjusted life-years; SEER: Surveillance Epidemiology and End Results; USD: United States dollar; UKLS: UK Lung Cancer Screening Trial.

2

4.4 Approach to the health economic assessment

The health economic assessment aims to investigate the cost-effectiveness and the potential budget impact of LDCT screening programs for lung cancer in high-risk populations in Switzerland.

The assessment will include a systematic review of the currently published cost-effectiveness evidence (including an adaptation of the cost results to Switzerland), an update of the Swiss cost-effectiveness analysis published in 2018 (Tomonaga et al.[76]), and a budget impact analysis (BIA) based on Swiss data.

4.4.1 Full systematic review of existing cost-effectiveness evidence

A systematic review of the current economic literature will be undertaken. The aim is to identify literature on the costs and cost-effectiveness of LDCT screening compared to no screening for subjects at high risk for developing lung cancer with emphasis on smokers and former smokers.

All types of economic evaluation studies will be considered and checked for relevant content: cost-effectiveness analyses, cost-benefit analyses, cost-utility analyses and cost-minimization analyses.

4.4.1.1 Literature search strategy

A search strategy to identify all relevant literature in the following electronic databases will be developed: Medline and Embase databases including abstracts by using OvidSP (including Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily Update, Embase), the Cochrane Library and the Centre for Review and Dissemination (CRD) database including the Database of Abstracts of Reviews of Effects (DARE), Cochrane reviews, Health Technology Assessments (HTA) and the Economic Evaluation Database from the UK National Health Service (NHS EED).

The literature search strategy will combine the clinical search strategy with a health economic search string. For the economic search strategy for Medline and Embase, the NHS EED filter will be used.[103] Because the NHS EED economic filter has not been published for Cochrane searches, the Medline NHS EED filter will be translated into a Cochrane search string with the help of an online application (Systematic Review Accelerator).[104] Minor adaptation will be applied if deemed necessary.

The period of search will be limited to the last ten years.

4.4.1.2 Screening of the search results

The results of the literature search will be screened by title, abstract and, if necessary, by full text review. In a first step, title and abstracts will be screened for relevant quantitative results (e.g. costs, LYG, QALYs, or ICERs) or for sentences suggesting potentially relevant content in the full text version.

Potentially relevant abstracts proceeded to the next step, in which full texts will be screened. Articles will then be classified in three groups:

- Relevant articles: full scale cost-effectiveness analyses using a PICO corresponding to the present scoping and reporting an endpoint of cost per QALY gained or cost per life-year gained. Ideally the analysis should be performed for a jurisdiction with broadly similar socioeconomic characteristics as Switzerland (e.g. North, Central, and Western European countries, the USA, Canada, Australia, and New Zealand).
- Articles potentially providing important additional information: articles not meeting the criteria for the 'relevant' category but potentially containing useful additional information

concerning effectiveness or costs, and thus being 'partially relevant'. Depending on the quality and quantity of information available from relevant articles, some partially relevant articles will be used as an additional source of information and for comparison.

- Irrelevant articles.

4.4.1.3 Assessment of quality and transferability

A brief, qualitative characterization of each relevant study will be prepared in the results section, covering methodological approaches taken, main data sources, methodological issues and potential meaningfulness of the results for Switzerland.

Quality of reporting will be assessed against the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 24-item checklist, recommended by the ISPOR Health Economic Evaluations Publication Guidelines Task Force.[105]

International cost-effectiveness studies will be assessed for 'qualitative transferability' to Switzerland. A variety of authors have worked on criteria for assessing such transferability between jurisdictions. Methodologic papers published by O'Brien et al., Welte at al., and Drummond et al. suggested the use of multistep procedures.[106-109] In the present study, a modified approach based on the above-mentioned procedures will be adopted.

The most important criteria for qualitative transferability are already covered by the eligibility criteria. Essentially, for the full-scale health economic evaluation, studies assessing incremental cost-effectiveness have to meet the 'PIC', or have to be performed for countries similar to Switzerland in terms of socioeconomic characteristics. Studies are thus expected to meet CHEERS criteria 4 (population), 7 (intervention / comparator[s]) and 10 (outcome measures).

In short, studies not meeting CHEERS items 4 (population), 5 (setting and location), 6 (study perspective), 7 (intervention/comparator), 8 (time horizon) , 10 (outcomes measures), 13 (estimating resources and costs), 14 (currency, price date, and conversion) and 19 (incremental costs and outcomes) will be regarded as not transferable due to lack of key information. In relation to item 19, the availability of costs and outcomes of interest for both the intervention and the comparator strategies will be considered fundamental.

4.4.1.4 Extraction of information

For the eligible cost-effectiveness studies (i.e. relevant articles as defined above), data extraction covering the following information will be performed:

- Study population (including country, characteristics of included subjects)
- Intervention (e.g. details on screening strategy)
- Comparator(s)
- Setting and perspective of the study
- Cost types included and cost year
- Type of model
- Time horizon
- Discount rate
- Approach to sensitivity analysis
- Effectiveness
- Costs
- Incremental cost-effectiveness ratio (ICER)

4.4.1.5 Adaptation of cost-effectiveness results to Switzerland

Cost results from qualitatively transferable studies will be adapted to Switzerland as described below, and adapted ICERs will be calculated on this basis. Effectiveness results will be used as reported.

The adaptation of the cost results will be performed in three distinct steps including (1) a correction for different levels of resource utilization, (2) a correction for different prices of healthcare services, and (3) a correction for change in level of resource utilization and prices over time.

It is important to emphasize that the results of such adaptation cannot be interpreted as achieving realistic ICERs for Switzerland, but a certain approximation of cost-effectiveness levels is to be expected for Switzerland. The results of international cost-effectiveness studies, reported for different countries and in different currencies, will be more comparable.

4.4.1.6 Synthesis of findings

The resulting different pieces of information will be synthesized. Comparisons of the assumptions and of the data used by the various cost-effectiveness analyses will be made. The discussion will include a critical review of possible sources of uncertainty.

4.4.2 Cost-effectiveness analysis

A Swiss cost-effectiveness analysis based on the MISCAN model was recently published.[76] A de novo cost-effectiveness analysis would require unreasonable time and resources, therefore adapting the existing model is considered the most efficient approach. This MISCAN-based analysis was calibrated using individual level-data from the NLST and the Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Screening Trial. The model was already adapted using Swiss specific input parameters regarding lung cancer epidemiology, smoking behaviours, and treatment costs. The effects and costs of 648 screening scenarios with different screening start and stop ages, smoking eligibility criteria, and screening intervals were examined from a public healthcare system perspective across a lifetime horizon in a cohort born between 1935 and 1965. The results suggested that several screening scenarios may be cost-effective in Switzerland, showing an ICER below CHF 50,000 per life-year gained.

The model will be updated with the effectiveness results of the NELSON trial (instead of NLST) and, if feasible, an update of all other Swiss input parameters (ranging from smoking behavior in Switzerland to lung cancer epidemiology and treatment costs). The improvement of the model will consist in implementing QALY estimates in the model and, if possible, potential effects of smoking cessation programs.

Since the use of the MISCAN model is covered by copyright, and since its structure cannot be freely changed, a close collaboration with the team of Prof. Harry de Koning of the Erasmus Medical Center in Rotterdam will be indispensable. The collaboration offers two major advantages. First, the MISCAN model is one of the most recognized lung cancer screening models developed on behalf of the U.S. National Cancer Institute. Second, Prof. Harry de Koning is the principal investigator of the NELSON trial, and hence, collaborating with the research group responsible for the NELSON trial may allow getting additional or unpublished trial information. The recently published 10 years results of the NELSON trial will contribute substantially to the update of the MISCAN model.

Prof. de Koning's team has expressed interest in collaborating with us on this project.

4.4.3 Cost-benefit and budget impact analyses

The aim of the cost-benefit and budget impact analyses (BIA) will be to investigate the economic impact of different LDCT screening strategies in comparison to no screening (or the current situation) in Switzerland. The overall costs of LDCT screening (in particular of LDCT and follow-up tests) will be compared to potential economic benefits (e.g. in terms of reduced treatment costs or productivity loss).

4.4.4 Perspective

Costs will be assessed from a third-party payers perspective. A societal perspective will be added only if possible.

4.4.5 Subgroup and sensitivity analyses

The cost-effectiveness analyses as well as the BIA will provide estimations for several study populations according to the screening inclusion criteria. This will automatically lead to cost and cost-effectiveness estimations for different subgroups according to smoking intensity, start and stop age of screening, and number of years since smoking cessation. If technically feasible, potential differences between gender will be investigated.

In the sensitivity analyses, parameter uncertainty will be addressed by varying sets of related inputs. These parameters include attendance rates, discounting rates, LDCT costs, and treatment costs. Attendance rate in the base case will be assumed to be 100%, whereas in the sensitivity analyses low (35%), average (50%), and high (65%) attendance rates will be assumed. Discounting, originally set at 3%, will be varied from 0% to 6%. Finally, LDCT and treatment costs will be varied by 30% if compared to the base-case estimations.

In case of a new cost-effectiveness analysis including the potential impact of smoking cessation therapies, a variation of the therapy effectiveness will be considered.

5 Ethical considerations

5.1 Context

The prospect of LDCT screening for lung cancer raises several ethical issues that require careful consideration. The ethical analysis in this HTA will be based upon the conclusions regarding clinical effectiveness and cost-effectiveness, and will consider patient and public perspectives on screening. The ethical issues listed in Table 5 are formulated very general and will be refined based on the findings from the two previous sections.

5.2 Ethical, legal and social issues

The following ethical issues will be included in the analysis (Table 5). Most of these issues concern those who might be invited to screening, but some concern the general population in Switzerland.

Table 5: Ethical issues according to population or public perspectives

Perspective of	Following ethical issues will be addressed
Population invited to screening	- Ethical issues concerning informed consent and shared decision making,particularly discussing and communicating potential risk and prospective benefits of screening with those invited to be screened (including importance of absolute vs relative risk). - Risk/benefit analysis from the perspective of the potentially screened person: potential clinical benefit vs false positives/distress/harm/side effects/incidental findings. - Issues in recruitment to screening – 'reluctant' patient population, stigmatisation. - Ethical issues in screening modalities: intervals, travel to hospital, radiation exposure, and smoking cessation. - Further ethical issues may be added if deemed relevant during assessment.
Wider public	- Issues in ethical resource allocation: does LDCT screening represent ethical/fair distribution of scarce resources? (Also covering the issue of who pays for screening). - Public perspectives on justice – for example, should those suffering from what is perceived as 'self-inflicted' disease be allocated resources funded by the whole population? (particularly given cost-effectiveness questions). - Further ethical issues may be added if deemed relevant during assessment.

5.3 Methods

5.3.1 Sources

The ethical analysis will be informed by:

- a systematic literature review by searching Medline via PubMed and additional purposive sampling of both ethics journals and medical journals, including qualitative research on public perspectives.

- the findings of the clinical effectiveness and cost-effectiveness assessment of this HTA report, which will also provide data on the specific Swiss context.
- and - only if insufficient literature is found - focus groups or public workshops to generate additional data on patient and public perspectives.

5.3.2 Ethical analysis

Ethical analysis of each of the issues identified in Section 5.2 and any others emerging from the literature review and/or the conclusions of the previous parts of the HTA regarding clinical effectiveness and cost-effectiveness. Each issue will be subjected to thorough normative analysis, applying the main principles of biomedical ethics (respect for autonomy, beneficence, nonmaleficence and justice)[110,111] and public health ethics.[112]

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