EUnetHTA Joint Action 3 2016-2020

Lung cancer screening in risk groups

Project ID: ***OTCA28***

Project description and planning

Institute for General Practice and Evidence-based Health Service Research (IAMEV), Medical University of Graz
&
HTA Austria - Austrian Institute for Health Technology Assessment GmbH (AIHTA)

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)

Galician Agency for Health Knowledge Management (Avalia-t; ACIS)

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Version Log

Version number	Date	Modification	Reason for the modification
V1	08/06/2020	1st version of draft project plan	-
V2	17/06/2020	Revised 2nd version of draft project plan	After comments from co-authors and dedicated reviewers
V3	30/06/2020	Revised 3rd version of draft project plan	After comments from external clinical experts

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1 Project organisation

1.1 Participants

Table 1-1: Project participants

	Agency	Role in the project	Country	Distribution of work
Assessment team				
1.	Institute for General Practice and Evidence-based Health Services Research, Medical University of Graz (IAMEV) On behalf of Austrian Institute for Health Technology Assessment GmbH (AIHTA)	Author	Austria	Develop first draft of the project plan. Develop first draft of the TEC/CUR domains of the assessment. Perform literature searches for PICO 4 and study selection for PICO 1 (other risk factors), 2 and 4. Carry out the assessment for PICO 1 on other risk factors (study selection, data extraction, analysis, synthesis, and interpretation of findings). Quality check the steps of assessment for PICO 1 on current and previous smokers. Carry out the assessment for PICO 3 for LDCT vs no (systematic) screening on persons with other risk factors and support the production of all domains and quality check the steps of their production for the remaining PICO 3 Carry out the assessments for PICO 2 and 4: (data extraction, analysis, synthesis, and interpretation of findings). Send “draft versions” to dedicated reviewers and external experts for comments, compile feedback from reviewers and experts, and incorporate relevant changes to the draft. Prepare final assessment including an executive summary.
2.	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)	Co-Author	Germany	Review the project plan draft. Perform literature search for PICO 1 and 2; provide lists of excluded references for PICO 1 (other risk factors). Carry out the assessment for PICO 1 on current and previous smokers (study

				selection, data extraction, analysis, synthesis, and interpretation of findings). Quality check the steps of assessment for PICO 1 on other risk factors. Carry out the assessment for PICO 3 for LDCT vs no (systematic) screening on current and previous smokers and support the production of all domains and quality check the steps of their production for the remaining PICO 3 Check, provide input and endorse content of all domains. Collaborate on the writing of the discussion and conclusions, and endorse these sections. Review drafts of the assessment including the executive summary.
3.	Galician Agency for Health Knowledge Management (Avalia-t; ACIS)	Co-Author	Spain	Review the project plan draft. Collect data on European Epidemiology of risk factors Perform a literature search on international guidelines regarding lung cancer screening. Support the production of all domains and quality check the steps of their production for PICO 2 and 4 (data extraction, analysis, synthesis, and interpretation of findings). Check, provide input and endorse content of all domains. Collaborate on the writing of the discussion and conclusions. Approve/endorse conclusions drawn as well as all draft versions and the final assessment including the executive summary.
4.	Regione Emilia-Romagna (RER)	Dedicated Reviewer	Italy	Guarantee quality assurance by thoroughly reviewing the project plan and the assessment drafts. Review methods, results, and conclusions based on the original studies included. Provide constructive comments in all the project phases
5.	University for Health Sciences, Medical	Dedicated Reviewer	Austria	Guarantee quality assurance by thoroughly

	Informatics and Technology (UMIT)			reviewing the project plan and the assessment drafts. Review methods, results, and conclusions based on the original studies included. Provide constructive comments in all the project phases
6.	Institute of Family Medicine and Public Health, University of Tartu (UTA)	Observer	Estonia	Review draft project plan, propose amendments where necessary and provide written feedback. Review assessments, propose amendments where necessary and provide written feedback.
Contributors				
7.	Giuseppe Gorini (specialist in epidemiology)	External clinical expert	Italy	Guarantee quality assurance by thoroughly reviewing the project plan and the assessment drafts. Review methods, results, and conclusions based on the original studies included. Provide constructive comments in all project phases.
8.	Giulia Picozzi (specialist in radiology)	External clinical expert		
9.	Vicenta Labrador Cañadas (Spanish Ministry of Health; head of population screening programs unit)	External clinical expert	Spain	
10.	Pilar Garrido López (specialist in oncology)	External clinical expert		
11.	Compuscript Ltd.	Medical Editor	Ireland	Medical editing
12.	Austrian Institute for Health Technology Assessment (AIHTA)	Project Manager	Austria	Project management

1.2 Project stakeholders

Table 1-2: Project stakeholders

Organisation	Role in the project
TBD	Patient representative

1.3 Milestones and Deliverables

Table 1-3: Milestones and Deliverables

Milestones/Deliverables	Start date	End date
Project duration	**04/05/2020**	**30/11/2020**
Scoping phase	**04/05/2020**	**30/06/2020**
Identification of manufacturer(s) and external experts; *optional: identification of patients*	04/05/2020	25/05/2020
Scoping and development of draft Project Plan incl. preliminary PICO	04/05/2020	19/05/2020
Share the preliminary PICO with external experts *(and patients)* for comments	19/05/2020	25/05/2020
Send the preliminary PICO for comments (in case there is no scoping meeting planned)	19/05/2020	25/05/2020
Internal Scoping e-meeting with the assessment team	04/06/2020	04/06/2020

Consultation of draft Project Plan with dedicated reviewers	09/06/2020	16/06/2020
Consultation of draft Project Plan with external experts *(and patients)*	17/06/2020	23/06/2020
Amendment of draft Project Plan & final Project Plan available	24/06/2020	30/06/2020
Assessment phase	**01/07/2020**	**30/11/2020**
Writing first draft rapid assessment	01/07/2020	17/08/2020
Review by dedicated reviewer(s)	20/08/2020	02/09/2020
Writing second draft rapid assessment	03/09/2020	23/09/2020
Review by ≥ 2 external clinical experts	24/09/2020	13/10/2020
Writing third draft rapid assessment	14/10/2020	30/10/2020
Medical editing	02/11/2020	11/11/2020
Writing of fourth version of rapid assessment	12/11/2020	20/11/2020
Formatting	23/11/2020	26/11/2020
Final version of rapid assessment		**30/11/2020**

2 Project Outline

2.1 Project Objectives

The rationale of this assessment is to collaboratively produce structured (rapid) core HTA information on other technologies. In addition, the aim is to apply those collaboratively produced assessments in the national or regional context.

Table 2-1: Project objectives

	List of project objectives	Indicator (and target)
1.	To jointly produce health technology assessments that are fit for purpose, of high quality, of timely availability, and cover the whole range of health technologies.	Production of 1 (rapid) relative effectiveness assessment.
2.	To apply this collaboratively produced assessment into local (e.g. regional or national) context.	Production of ≥2 local (e.g. national or regional) reports based on the jointly produced assessment.

Lung cancer is one of the most common diagnosed cancers and affects more than 300.000 people every year in the European Union. It is also the leading cause of cancer death. In 2012 the age-standardized rate in Europe was 24.7 deaths per 100.000 people [1]. The main risk factor for developing lung cancer is smoking [2]. It is estimated that 85% of lung cancer is attributed to active smoking [3]. Other risk factors are environmental or occupational exposures to harmful substances like asbestos or radon gas, or fine particle exposure [4, 5]. In addition, people with a history of lung disease like chronic obstructive pulmonary disease (COPD) or pulmonary fibrosis have an increased risk for lung cancer [6]. Symptoms of lung cancer are unspecific and therefore lung cancer is usually detected late. About 70% of the patients are diagnosed at an advanced or metastatic stage [1]. Screening for lung cancer might help to detect lung cancer in earlier stages. Until recently, no organised screening programs for lung cancer existed in Europe [7, 8]. US guidelines recommend lung cancer screening programs with annual screening using low-dose computed tomography (LDCT) [6, 9]. Furthermore, biomarkers are under investigation as additional screening tools [10].
This rapid assessment addresses the topic of lung cancer screening in risk groups (persons with history of smoking or current smokers, persons with occupational or environmental exposure to radon, asbestos or fine particles, patients with COPD or lung fibrosis, or persons with a family history of lung cancer). For this purpose four research questions were defined:

- Research question 1: What is the benefit/harm of screening for lung cancer using low-dose computed tomography (LDCT) compared to no (or no systematic) screening in individuals at elevated risk of lung cancer? As there is reason to assume comparability of no screening and screening using chest x-ray, screening for lung cancer using chest x-ray will be taken into account as a comparator, too if reasonable.
- Research question 2: What is the benefit/harm of screening for lung cancer using biomarkers in addition to LDCT compared to screening using LDCT alone in individuals at elevated risk of lung cancer?
- Research question 3: What is the benefit/harm of organizational variations of systematic screening for lung cancer using LDCT (e.g. screening with different intervals, with/without invitation) on individuals at elevated risk of lung cancer?
- Research question 4: What is the best strategy to inform individuals in the target group about a lung cancer screening program to optimize an informed choice regarding participation?

This topic is part of the Austrian national work programme and also of the Spanish Network of HTA Agencies (RedETS) annual work plan. Results will be used by the Austrian screening committee and by the Spanish population screening committee.

2.2 Project Method and Scope

2.2.1 Approach and Method

Table 2-2: Project approach and method

Project approach and method
The HTA Core Model Application for rapid Relative Effectiveness Assessment (REA) (4.2) will be the primary source for selecting assessment elements. The selected assessment element generic questions will be translated into research questions. Description and technical characteristics of technology (TEC) and Health problem and current use of technology (CUR) domains For TEC and CUR domains a descriptive analysis will be performed, based on information from current clinical guidelines, review articles and input from clinical experts. The assessment will focus on the entire process of lung cancer screening and not on the evaluation of a single diagnostic or therapeutic product or technology. It is planned to describe the different screening algorithms or modalities (e.g. risk and age groups, screening intervals, the role of biomarkers, follow up diagnostic and therapeutic procedures) currently used. Effectiveness (EFF) and Safety (SAF) domains The assessment of research question 1 will be based on a current national assessment report on benefit and harms of screening for lung cancer using low-dose computed tomography (LDCT) in persons with history of smoking or current smokers without suspected lung cancer (report number S19-02) conducted by one of the co-authors (IQWiG) [11]. This report will be extended to other risk factors for lung cancer (i.e. occupational exposure to radon, asbestos or fine particles, COPD, lung fibrosis, family history of lung cancer). For the research question 2 the results from the literature search for research question 1 will be used to identify studies on lung cancer screening using biomarkers in addition to LDCT. An additional systematic literature search focusing on biomarkers for lung cancer screening will be performed. For the research question 4 a separate systematic literature search will be performed. For all research questions all selection steps will be performed by 2 persons of the author or co-authors independently of each other. Discrepancies will be resolved by discussion. For population 1 (current and previous smokers) of research question 1 process steps have already been / will be done by 2 persons of one of the co-authors. An additional reviewer of the author will check the whole processes, including the assessments. Two persons of the author will do the process steps for population 2 (persons with other potential risk factors) of research question 1 and for research question 2. An additional reviewer of the co-authors will check the whole process, including the assessments. For research question 4 the study selection steps will be performed by 1 person of the author and 1 person of the co-authors. For research question 3, all studies included in research question 1 and 2 will be used and subgroup analysis on different screening modalities will be performed. Study and outcomes validity and level of evidence will be assessed according to the EUnetHTA guideline for internal validity of randomised controlled trials [12]. As recommended in this guideline the Risk of bias (RoB) assessment of the included studies will be done according to the Cochrane Risk of bias tool [13] on study and outcome level. The 'Risk of bias' of each included trial will be assessed by the author and the co-authors independently. Any disagreements will be resolved by consensus or by consulting a third party (dedicated reviewers). The quality of the body of evidence will be assessed using GRADE (Grading of Recommendations, Assessment, Development and Evaluation) [14]. The results of the rating will be presented in GRADE Summary of Findings (SoF)

tables. The author will perform the GRADE rating and the co-authors will check it. Disagreements will be resolved by consensus.

When at least two included randomised controlled trials (RCTs) are available for a comparison and a given outcome, with a similar length of intervention and a similar follow-up time after the screening, we will perform meta-analysis. The estimated effects and confidence intervals from the studies will be summarized using forest plots. Dichotomous data will be expressed as a risk ratio (RR) or odds ratio (OR) with 95% confidence interval (CI). For continuous outcomes measured on the same scale we will estimate the intervention effect using the mean difference with 95% CI. For continuous outcomes that measure the same underlying concept (e.g. health-related quality of life) but use different measurement scales, we will calculate the standardised mean difference (SMD).

If possible, we obtain relevant missing data from the authors of the included trials. We carefully evaluate important numerical data such as screened, randomised assigned participants as well as intention-to-treat (ITT), and as-treated and per-protocol populations. We investigate attrition rates (e.g. drop-outs, losses to follow-up, withdrawals), and we critically appraise issues of missing data and imputation methods (e.g. last observation carried forward (LOCF)).

We consider fixed-effect and random-effects models for the meta-analyses. We use the Q-Test for assessing heterogeneity. If the heterogeneity of study results is not relevant (e.g. p-value for heterogeneity statistics ≥ 0.05) then the common (pooled) effect including the confidence interval will be presented. In the event of relevant heterogeneity, the results will be pooled only in justified exceptional cases.

Where included trials do not report means and SDs for outcomes and we will not receive the necessary information from trial authors, we will impute these values by estimating the mean and variance from the median, range, and the size of the sample [15].

If possible, following subgroup analyses will be performed:

- age groups
- sex
- strength of exposure with tobacco or occupational toxins
- screening strategy (e.g. screening interval)

To evaluate the robustness of results, the assessment may include sensitivity analyses with regard to methodological factors. According to a sensitivity analysis, for PICO 1 studies with chest-x-ray as a comparator will also be taken into account.

Table 2-3: Planned literature search strategy

Literature search strategy
<u>Description and technical characteristics of technology (TEC) and Health problem and current use of technology (CUR) domains</u> • Clinical guidelines: A systematic literature search for current clinical guidelines in various guideline databases will be performed. • Non-systematic literature search for prevalence rates for different lung cancer risk factors across Europe and for lung cancer rates in exposed groups. • Relevant literature identified by the literature search for the EFF and SAF domains. No quality assessment of the included literature will be conducted for these two domains. • Input from clinical experts, particularly related to description of disease, current treatment, current use and best available epidemiological data. The clinical experts will be asked to verify the relevance and accuracy of the information and citations.

Effectiveness (EFF) and Safety (SAF) domains:

For the **research questions 1** the results of the national benefit-harm assessment report on screening for lung cancer using low-dose computer tomography (LDCT) in persons with history of smoking or current smokers (report number S19-02) conducted by one of the co-authors (IQWiG) [11] will be used. In this report a systematic literature search for relevant systematic reviews was conducted in the bibliographic databases Medline, Cochrane Database for Systematic Reviews and Health Technology Assessment Database. The search was restricted to the last 6 years before 2019 and to articles published in English or German.

In addition, for time periods not covered by relevant systematic reviews, systematic literature searches for RCTs were conducted in the following databases: Medline, Embase, and Cochrane Central Register of Controlled Trials. Furthermore, a search in the clinical trials registries ClinicalTrials.gov and WHO-ICTRP was carried out for ongoing or unpublished studies. In addition to the electronic search, the references from included original articles and reviews were reviewed and authors of potentially relevant studies were contacted.

This report will be extended to other risk factors for lung cancer (i.e. occupational or environmental exposure to harm substances, COPD, lung fibrosis, family history of lung cancer). Therefor the list of excluded studies from the IQWiG report will be re-screened, to identify studies on these risk factors. In addition, all studies already included for research question 1 will be checked regarding the proportion of people reporting other exposures and results for these subgroups will be extracted, if possible. If necessary, additional systematic literature searches will be performed for risk factors other than smoking in the bibliographic databases MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials and Cochrane Database for Systematic Reviews, according to the predefined search strategies.

Furthermore, a search in the clinical trials registries ClinicalTrials.gov and WHO-ICTRP will be carried out for ongoing or unpublished studies.

In addition to the electronic search, we will review the references from included original articles and reviews.

For **research question 2** the list of excluded studies from the IQWiG report will be re-screened, to identify studies on lung cancer screening using biomarkers in addition to LDCT. In addition a systematic literature search will be performed for biomarkers in lung cancer screening in the bibliographic databases MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials and Cochrane Database for Systematic Reviews, according to the predefined search strategies. Furthermore, a search in the clinical trials registries ClinicalTrials.gov and WHO-ICTRP will be carried out for ongoing or unpublished studies.

For **research question 3**, no separate information retrieval is carried out, but the screening result from PICO 1 and 2 is used.

For research questions 4 we will perform independent systematic literature searches in the bibliographic databases MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials and Cochrane Database for Systematic Reviews, according to the predefined search strategies.

In addition to the electronic search, we will review the references from included original articles and reviews.

Inclusion criteria:

According to the PICO questions 1 to 4 summarized in table 2-5

Exclusion criteria:

- Languages other than English or German as per IQWIGs report for question 1 to 3
- Languages other than English, German or Spanish for question 4

- Publications of clinical trials not meeting the Consolidated Standards of Reporting Trials (CONSORT) criteria [16]
- In addition for research question 1 to 3 we will exclude study designs other than RCTs

Data management:

- Endnote X8 will be used for citation management
- Study selection will be performed in IQWiG's internal web-based trial selection database (webTSDB).

Table 2-4: Plan for data extraction

Planned data extraction
Effectiveness (EFF) and Safety (SAF) domains: Data to be extracted from the studies include: • Study characteristics (authors, year of publication, setting/country, inclusion criteria, study design, study duration, primary study endpoint, clinical trial identification number/ registry identifier and funding source) • Participant/patient characteristics (number of participants in the trial, age, sex, characterisation of risk factor) • Intervention and control characteristics (name/type of the technology, screening strategy and regimen [e.g. number of rounds, screening interval, radiological protocol, definition of positive tests], recruitment/invitation process, co-intervention [e.g. smoking cessation interventions], length of the intervention (screening), length of follow up after screening and person flow [e.g. adherence, contamination, frequency of invasive diagnostics] • Outcomes: o Research questions 1-3: mortality (overall mortality, lung cancer mortality), morbidity (stage distribution of lung cancer), health-related quality of life, harms resulting from screening itself or from subsequent diagnostic interventions (e.g. invasive biopsy) including overdiagnoses[1], consequences resulting from false screening results (false positive and false negative) or from unclear findings; (serious) adverse events o Research question 4: informed decision-making, participant satisfaction, participant empowerment Mortality (overall mortality, lung cancer mortality) is classified as a critical outcome, all other outcomes as important.

2.2.2 Project Scope

The EUnetHTA Guidelines, available at https://www.eunethta.eu/methodology-guidelines/ **need to be consulted** throughout the assessment process.

Table 2-5: Project Scope: PICO 1 (please see HTA Core Model® for rapid REA)

Description	Project Scope
Population	Adult persons (age 18 and older) without lung cancer (confirmed or suspected) (ICD-10 code C34) at elevated risk of lung cancer.

[1] Defined as number of diagnoses (true positive findings), which would not have become clinically relevant during a person´s lifetime

	Population 1: Persons with history of smoking or current smokers Population 2: Persons with other potential risk factors: occupational or environmental toxins (e.g. radon, asbestos or fine particle exposure), COPD (ICD-10 code J44), lung fibrosis (ICD-10 code J84.1; J68.4; J70.1), family history of lung cancer (ICD-10 code C34) Further subgroups identified in the literature will also be included
Intervention	Systematic screening for lung cancer using low-dose computed tomography (LDCT)
Comparison	No (systematic) screening (usual care). According to a sensitivity analysis, screening for lung cancer using chest x-ray will be taken into account as an additional comparator for the outcomes mortality and consequences resulting from overdiagnoses, too. Rationale: Results of the PLCO study [17] give reason to assume comparability of no screening and screening using chest x-ray.
Outcomes	• Mortality (overall mortality, lung cancer mortality) • Morbidity • Health-related quality of life • Harms resulting from screening itself (e.g. consequences from radiation exposure[2]) or from subsequent diagnostic interventions (e.g. invasive biopsy) including overdiagnoses[3], consequences resulting from false screening results (false positive and false negative) • (Serious) adverse events
Study design	Randomised controlled trials (RCTs)

Table 2-6: Project Scope: PICO 2 (please see HTA Core Model® for rapid REA)

Description	Project Scope
Population	*See PICO 1 (table 2-5)*
Intervention	Screening for lung cancer using biomarkers in addition to low-dose computer tomography (LDCT) a) Biomarkers can be used as a test for the selection of people undergoing screening b) Biomarkers can be used as a test for characterization of undetermined nodules found during the CT-based screening.
Comparison	Screening for lung cancer using LDCT alone Rationale: LDCT alone is the recommended screening intervention according to current guidelines.
Outcomes	*See PICO 1 (table 2-5)*
Study design	*See PICO 1 (table 2-5)*

[2] Based on the results of the assessment report of the German "Bundesamt für Strahlenschutz"
[3] Defined as number of diagnoses (true positive findings), which would not have become clinically relevant during a person's lifetime

Table 2-7: Project Scope: PICO 3 (please see HTA Core Model® for rapid REA)

Description	Project Scope
Population	*See PICO 1 (table 2-5)*
Intervention	Annual systematic screening for lung cancer using LDCT as recommended in guidelines
Comparison	Systematic screening for lung cancer using LDCT different in screening interval (shorter or longer) or type of systematic screening (organizational variants, e.g. with invitation)
Outcomes	*See PICO 1 (table 2-5)*
Study design	*See PICO 1 (table 2-5)*

Table 2-8: Project Scope: PICO 4 (please see HTA Core Model® for rapid REA)

Description	Project Scope
Population	*See PICO 1 (table 2-5)*
Intervention	Specific information strategy for lung cancer screening (e.g. content, mode of distribution)
Comparison	A specific information strategy for lung cancer screening different from the one used in the intervention group (e.g. different content, different mode of distribution) or no specific information strategy for lung cancer screening
Outcomes	• Screening participation rate • Participant satisfaction • Participant empowerment • Increased knowledge • Informed decision-making
Study design	Systematic reviews; Randomised controlled trials (RCTs); Non-randomised controlled trials; Prospective observational studies; Qualitative studies

3 Communication and collaboration

Table 3-1: Communication

Communication Type	Description	Date	Format	Participants/ Distribution
Scoping	Internal kick-off meeting	19/05/2020	E-meeting	Author(s), co-author(s), dedicated reviewers, observers, project manager
	Scoping e-meeting	04/06/2020	E-meeting	Author(s), co-author(s), dedicated reviewers, observers, project manager
	To internally discuss and reach consensus on the scoping.	19/05/2020-30/06/2020	E-mail	Author(s), co-author(s), dedicated reviewers, observers, project manager
		As required	*Additional e-meetings may be planned whenever needed*	*Author(s), Co-author(s), dedicated reviewer(s), project manager*
First draft of the rapid assessment	*To discuss comments of dedicated reviewers*	*03/09/2020-23/09/2020*	*E.mail E-meetings may be planned*	*Author(s), co-author(s), dedicated reviewers*
Second draft of the rapid assessment	*To discuss comments from ≥2 external clinical experts*	*As required*	*E-meetings may be planned*	*Author(s), co-author(s), dedicated reviewers; external experts*

3.1 Dissemination plan

The final rapid assessment will be published on the EUnetHTA website: http://eunethta.eu/rapid-reas/ .

All stakeholders and contributors are informed about the publication of the final assessment by the project manager.

3.2 Collaboration with stakeholders

Collaboration with manufacturer(s)

No manufacturers are included in the preparation of this Rapid REA. This is due to the fact that the technology under assessment is the screening process itself. Therefore, the focus is not on the evaluation of a single diagnostic or therapeutic product or technology.

Collaboration with other stakeholders

Patient involvement was planned and patient organizations for chronic obstructive pulmonary disease (COPD) from Germany and Ireland were contacted to provide input on the draft PICO questions. However it was not possible to obtain participation.

3.3 Collaboration with EUnetHTA WPs

For the individual rapid assessment, some collaboration with other WPs is planned: WP7 [Implementation] will be informed of the project, in order to prepare activities to improve national uptake of the final assessment. Feedback on the WP4 REA process will be asked from the involved parties by WP6 [Quality Management], and this information will be processed by WP6 to improve the quality of the process and output.

3.4 Conflict of interest and confidentiality management

All authors, co-authors, dedicated reviewers, observers, external experts (health care professionals, patients or patient representatives) involved in the production of this assessment have declared they have no conflicts of interest in relation to the technology and comparator(s) assessed according to the EUnetHTA declaration of interest (DOI) form, which was evaluated following the EUnetHTA Procedure Guidance for handling DOI form (https://eunethta.eu/doi).

4 References

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Appendix A

4.1 Selected Assessment Elements

The table shows the assessment elements and the translated research questions that will be addressed in the assessment. They are based on the assessment elements contained in the 'Model for Rapid Relative Effectiveness Assessment'. Additionally, assessment elements from other HTA Core Model Applications (for medical and surgical interventions, for diagnostic technologies or for screening) have been screened and included/ merged with the existing questions if deemed relevant.

Table 4-1: Selected Assessment Elements

ID	Topic	Topic Issue	Relevance in this assessment [**Yes – critical**, **Yes** or **No**]	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
Description and technical characteristics of technology					
B0001	Features of the technology and comparators	What is the technology and the comparator(s)?	Yes	M	What is lung cancer screening? Which technologies are used for lung cancer screening?
A0020	Regulatory Status	For which indications has the technology received marketing authorisation or CE marking?	Yes	M	For which indications have each of the used screening technologies received CE-marking?
B0002	Features of the technology and comparators	What is the claimed benefit of the technology in relation to the comparator(s)?	Yes	M	What is the claimed benefit of lung cancer screening in relation to no screening? What might be the potential harms or risks of lung cancer screening in relation to no screening?
B0003	Features of the technology	What is the phase of development and implementation of the technology and the comparator(s)?	Yes	NM	What is the phase of development and implementation of each of the used screening technologies?
B0004	Features of the technology	Who administers the technology and the comparator(s) and in what context and level of care are they provided?	Yes	M	Who administers the technologies used for lung cancer screening? In what context is lung cancer screening provided? In what setting is it used?
B0008	Investments and tools required to use the technology	What kind of special premises are needed to use the technology and the comparator(s)?	Yes	NM	What kind of special premises are needed for lung cancer screening?
B0009	Investments and tools required to use the technology	What equipment and supplies are needed to use the technology and the comparator(s)?	Yes	NM	What equipment and supplies are needed for lung cancer screening?
B0013	Training and information needed to use the technology	What kinds of skills and training characteristics and information are needed for the personnel/caregivers using this technology?	Yes	NM	What kinds of skills and training characteristics and information are needed for the personnel/caregivers performing lung cancer screening?
A0021	Regulatory Status	What is the reimbursement status of the technology?	No	NM	-
Health problem and current use of technology					
A0002	Target Condition	What is the disease or health condition in the scope of this assessment?	Yes	M	How is lung cancer defined? What are the different forms and stages of lung cancer?
A0003	Target Condition	What are the known risk factors for the disease or health condition?	Yes	M	What are the most common risk factors for lung cancer? How are they defined
A0004	Target Condition	What is the natural course of the disease or health condition?	Yes	M	What is the natural course of lung cancer?

ID	Topic	Topic Issue	Relevance in this assessment [Yes – critical, Yes or No]	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
A0005	Target Condition	What are the symptoms and the burden of disease or health condition for the patient?	Yes	M	What are the symptoms and burden of disease of lung cancer?
A0006	Target Condition	What are the consequences of the disease or health condition for the society?	No	NM	
A0024	Current Management of the Condition	How is the disease or health condition currently diagnosed according to published guidelines and in practice?	Yes	M	How is lung cancer currently diagnosed according to published guidelines and in practice?
A0025	Current Management of the Condition	How is the disease or health condition currently managed according to published guidelines and in practice?	Yes	M	How is lung cancer currently managed according to published guidelines and in practice?
A0007	Target Population	What is the target population in this assessment?	Yes	M	What is the target population in this assessment?
A0023	Target Population	How many people belong to the target population?	Yes	M	How many people belong to the target population?
A0011	Utilisation	How much are the technologies utilised?	No	NM	-
Clinical effectiveness					
D0001	Mortality	What is the expected beneficial effect of the intervention on mortality?	Yes	M	What are the expected beneficial effects of lung cancer screening and the used technologies on overall mortality? What are the expected beneficial effects of lung cancer screening and the used technologies on lung cancer mortality?
D0005	Morbidity	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?	Yes	M	How do lung cancer screening and the used technologies affect the occurrence of lung cancer?
D0006	Morbidity	How does the technology affect progression (or recurrence) of the disease or health condition?	Yes	M	How do lung cancer screening and the used technologies affect the progression of lung cancer? How do lung cancer screening and the used technologies affect the stage distributions of lung cancers?
D0011	Function	What is the effect of the technology on patients' body functions?	Yes	M	What are the effects of lung cancer screening and the used technologies on patients' body functions?
D0016	Function	How does the use of technology affect activities of daily living?	No	NM	-
D0012	Health-related quality of life	What is the effect of the technology on generic health-related quality of life?	Yes	M	What are the effects of lung cancer screening and the used technologies on generic health-related quality of life?
D0013	Health-related quality of life	What is the effect of the technology on disease-specific quality of life?	Yes	M	What are the effects of lung cancer screening and the used technologies on lung cancer specific health-related quality of life?
D0030	Quality of life	Does the knowledge of the test result affect the patient's non-health-related quality of life?	Yes	NM	Does the knowledge of the test result affect the patient's non-health-related quality of life?
D0017	Patient satisfaction	Were patients satisfied with the technology?	Yes	NM	Were patients satisfied with lung cancer screening and the used technologies?

ID	Topic	Topic Issue	Relevance in this assessment [Yes – critical, Yes or No]	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
D0020	Change-in-management	Does use of the test lead to improved detection of the condition?	Yes	NM	Does lung cancer screening lead to improved detection of lung cancer?
H0202	Communication aspects	How are treatment choices explained to patients?	Yes	M	How are treatment choices explained to patients?
H0203	Communication aspects	What specific issues may need to be communicated to patients to improve adherence?	Yes	M	What specific issues may need to be communicated to patients to improve adherence?
Safety					
C0008	Patient safety	How safe is the technology in relation to the comparator(s)?	Yes	M	How safe are lung cancer screening and the used technologies in relation to no screening?
C0002	Patient safety	Are the harms related to dosage or frequency of applying the technology?	Yes	NM	Are the harms related to the frequency of lung cancer screening? Are the harms related to dosage of applying the technologies used for screening?
C0004	Patient safety	How does the frequency or severity of harms change over time or in different settings?	No	M	-
C0005	Patient safety	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?	Yes	M	What are the susceptible person groups that are more likely to be harmed through lung cancer screening or the technologies used for screening?
C0006	Patient safety	What are the consequences of false positive, false negative and incidental findings generated by using the technology from the viewpoint of patient safety?	Yes	M	What are the consequences of false positive, false negative and incidental findings generated by lung cancer screening from the viewpoint of patient safety?
C0007	Patient safety	Are the technology and comparator(s) associated with user-dependent harms?	No	NM	-
B0010	Safety risk management	What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator(s)?	No	NM	-

4.2 Checklist for potential ethical, organisational, patient and social and legal aspects

1. Ethical	
1.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new ethical issues?	Yes
The introduction of a screening program can provide a benefit only to a relatively small group of people (people with undetected lung cancer), but potentially provides harm to all people participating in the screening program.	
1.2. Does comparing the new technology to the defined, existing comparators point to any differences that may be ethically relevant?	No
2. Organisational	
2.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) require organisational changes?	Yes
The introduction of a screening program will result in additional costs. It will also potentially lead to a reorganisation of resources and structures.	
2.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be organisationally relevant?	No
3. Social	
3.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new social issues?	Yes
Since screening is offered only to persons with elevated risk for lung cancer (e.g. smokers), screening participants might be stigmatized.	
3.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be socially relevant?	No
4. Legal	
4.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any legal issues?	No
4.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be legally relevant?	No