"Effect of breast cancer screening in the Republic of Moldova"

Published by National Public Health Agency (NPHA)
Title Effect of breast cancer screening in Republic of Moldova
Moldovan title Eficiența screening-ului cancerului glandei mamare
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ISBN

ISSN
Report
Project number
Type of report Health Technology Assessment
No. of pages
Commissioner

Subject Breast cancer screening

MeSH terms
brest neoplasm; mammography; xeromammography; ultrasonography, mammary; magnetic resonance imaging; diffusion magnetic resonace imaging; diffusion tensor imaging; echo-planar imaging; mass screening-methods; ages factors; female; breast neoplasm –prevention&control; diagnosis, differential; review.

Citation

Table of content

Key messages

In the Republic of Moldova, breast cancer accounts for 17% of the total number of cancer cases with more than 1000 new cases added each year for a prevalence of over 10,000 patients in a population of 2.6 million. More than 32.5% of women diagnosed with BC in 2019 were in stages III-IV.

European Guidelines recommend implementing mammography screening over no mammography screening in the 50-69 years age group (strong recommendation). RCTs that compared invitation to mammography screening with no invitation showed reduced breast cancer mortality in women 50-69 years and 70-74 years (high certainty of evidence) but not in women <50 years (moderate certainty of evidence).

Based on health economic evaluation, total treatment costs for the 1,151 new cases of BC in 2019 could rise up to 34 605 487 MDL. Upon conducting a BCS Program in projected settings, costs could be reduced by at least 1 million MDL a year.

High certainty of evidence evidence indicates clinical benefits of screening in terms of preventing premature deaths due to breast cancer. The age range that has the maximum benefit from screening is 50-69 years.

Executive summary

Background

In the Republic of Moldova more than 1,000 new cases of breast cancer are detected each year. This is more than 11.0% of annual morbidity from oncologic diseases. It is expected that 1 out of 9 women during her lifespan will acquire breast cancer. In the last five years only 15.7-21.2% of new cases of breast cancer have been detected by regular medical check-up. Breast cancer accounts for 17% of the total number of cancer cases in the country, the incidence in 2019 was 1,151 new cases, and the prevalence is approximately 10,000 patients in a population of 2.6 million. Total treatment costs for the 1,151 new cases in 2019 could rise up to 34 605 487 MDL (1 730 274 Euro).

In Moldova breast cancer screening (BCS) started in October 2018, and has not been submitted to any kind of evaluation so far. A pilot health technology assessment (HTA) was initiated by the National Public Health Agency (NPHA) on this topic selected by the Ministry of Health, Labor and Social Protection (MHLSP) to assess the effects of breast cancer screening in the Republic of Moldova. NPHA has conducted the pilot HTA with the support from the Norwegian Institute of Public Health (NIPH) with the aim of determining clinical effects and costs of performing breast cancer screening in the current setting in the Republic of Moldova to inform what age groups should be included in the upcoming revised protocol of the screening program.

Methods

Health technology assessment (HTA) refers to the systematic evaluation of properties, effects, and/or impacts of a health technology. It is a multidisciplinary process to evaluate the clinical effectiveness and safety, as well as social, economic, organizational and ethical issues of a health intervention or health technology. The research question was determined using the so-called PICOS (Population-Intervention-Comparator-Outcome-Study) design which was basis for the inclusion criteria.

The team decided to select the following PICO:

- Population: Asymptomatic women aged 40-75;
- Intervention: Imaging technology (mammography and 3D mammography, MR, Ultrasound);
- Comparator: No screening;

- Outcome: All cause mortality, Breast cancer-related mortality, HRQoL, Harms (false positives or true positives, but treated without increased survival) including anxiety, overdiagnosis, and overtreatment.

We performed literature searches for systematic reviews in the databases Epistemonikos, PubMed and the Cochrane Database of Systematic Reviews. In addition, we carried out a search for international guidelines (i.e. SRs therein) in different electronic databases and websites. Selection and final inclusion of the literature followed the PRISMA recommendations. Quality assessment of included literature was done using the AMSTAR-2 check-list and certainty of estimates was assessed using the GRADE approach.

Health economic evaluation

The budget impact of breast cancer screening was analysed from a provider perspective, to estimate the current and projected costs of screening and breast cancer treatment in Moldova, based on available data on screening and treatment protocols.

Clinical effectiveness

Selection of the literature

A total of 2,365 records from three major databases (Epistomonikos, Cochrane and Pubmed) were identified and 318 duplicates and 2,047 records as not relevant to PICOS were removed for a total of potentially 23 relevant publications to be assessed further. A total of 1,761 guidelines were identified and 107 duplicates and 1,595 guidelines as not relevant to PICOS were removed for a total of potentially five relevant guidelines to be assessed further. These were selected for further evaluation and quality assessment using the AMSTAR-2 tool. The most recent SR(s) assessed to be of high quality (and covering all our predefined outcomes) was finally included.

Of note, as this review process was initiated prior to the publication of the European Guidelines, the team had initially decided to include three SRs, therefore, the team decided to include the SRs from the newly published European guidelines and to present the GRADE assessments already done in these.

Description of included literature

The European guidelines on breast cancer screening and diagnosis and recommendation on mammography screening for women were developed by the Joint Research Centre (JRC) coordinated by the European Commission's Initiative on Breast Cancer (ECIBC). The technical report, i.e. the systematic reviews the guidelines are based on are not yet publically available, but we have used the technical report upon permission from the authors from JRC.

The technical report by JRC includes a systematic review of the evidence of the effects of mammography screening on breast cancer mortality and morbidity in women under the age of 50, 50-69 age group and 70 years and older. The literature search was last performed in April 2016 in the databases MEDLINE, EMBASE and Central. JRC reviewers included 25 publications from the eight RCTs, and three systematic reviews

from observational studies that assessed the psychological and procedures impact of false positive results in the context of organized breast screening program (28 publications in total). The quality of the SR on effect of BCS in the JRC technical report was assessed by the authors to be of high methodological quality using the AMSTAR-2 checklist.

Results by outcome (from the JRC technical report)

Breast cancer related mortality

- Eight RCTs including totally 152,344 screened women assessed the effect of BCS within the age range 40-49 years. Screening probably does not reduce breast cancer mortality as observed after a mean of 15.2 years of follow-up. RR=0.92 (95% CI 0.83-1.02) with moderate certainty of evidence of evidence (GRADE ⊕⊕⊕◯).
- Six RCTs including in total 134,866 screened women assessed the effect of BCS within the age range 50-69 years. Screening reduces breast cancer mortality as observed after a mean of 15.5 years of follow-up. RR=0.77 (95% CI 0.67-0.88 with high certainty of evidence (GRADE ⊕⊕⊕⊕).
- Two RCTs including 7,598 screened women assessed the effect of BCS within the age range 70-74 years. Screening reduces breast cancer mortality as observed after a mean of 20.0 years of follow-up. RR=0.77 (95% CI 0.54-1.09) with high certainty of evidence (GRADE ⊕⊕⊕⊕).

Other cause mortality

- Six RCTs including totally 120,225 screened women assessed the effect of BCS within the age range 40-49 years. We do not know if screening reduces other cause mortality as observed after a mean of 10.8 years of follow-up. RR=1.04 (95% CI 0.95 to 1.15) with very low certainty of evidence (GRADE ⊕◯◯◯).
- Three RCTs including totally 66,432 screened women assessed the effect of BCS within the age range 50-69 years. Screening may not reduce other cause mortality as observed after a mean of 9.6 years. RR=0.99 (95% CI 0.95 to 1.04) with low certainty of evidence (GRADE⊕⊕◯◯).
- Two RCTs including totally 10,339 screened women assessed the effect of BCS within the age range 70-74 years. Screening may not reduce other cause mortality as observed after a mean of 7.9 years. RR=1.01 (95% CI 0.91 to 1.10) with low certainty of evidence (GRADE⊕⊕◯◯).

Overdiagnosis (woman perspective)

Overdiagnosis (woman perspective) occurred in 22.7% of examined cases (95% CI 18.4%-27.0%; 1 RCT and 1 observational study) in the age group 40-49 with moderate certainty of evidence (GRADE ⊕⊕⊕◯). Overdiagnosis (woman perspective) occurred in 17.3% of examined cases (95% CI 14.7%-20.0%; 2 RCTs) in the age group 50-69 and 70-74 with moderate certainty of evidence (GRADE ⊕⊕⊕◯).

Quality of life (inferred from psychological effects)

Anxiety in screened women appears to not increase if the procedures are clear and transparent, and the results are presented to them in a clear way. For women who are recalled the levels of anxiety may rise and subsequently the quality of life diminish at least for the waiting period (certainty of evidence low ⊕⊕◯◯ for all age ranges).

False-positive related adverse effects

Four observational studies assessed the false-positive effects on 390,000 screened women aged 50 to 69 with focus on biopsies and surgeries undertaken after BCS. Results showed an overall false-positive rate of 19.7% in women undergoing 10 biennial screening tests (pooled risk estimate based on 3 studies; range 8-21%); also 2.2% and 1.1% of all screening examinations resulted in needle biopsy among women without breast cancer (initial and subsequent screens, respectively). In addition, 0.19% and 0.07% of all screening examinations resulted in surgical interventions among women without breast cancer (initial and subsequent screens, respectively). Certainty of the estimates were very low (⊕◯◯◯) according to the GRADE assessment.

Health economic evaluation

Between October 2018 and December 2019, there were 18,109 mammograms (only screening mammograms included) performed in the target population. Based on official data on cost per procedure, we estimated the variable costs of the current screening programme (incurred up to December 2019) to be 8 447 016 MDL/422 350 Euro. The total cost comprises of the following: 1) cost of performing 18,109 mammograms estimated at 5 668 117 MDL (283 406 Euro); cost of recalls (at 16% of mammograms costs) – 906 899 MDL (45 345 Euro); cost purchase of 4 mobile units used for BCS – 1 872 000 MDL (93 600 Euro)

Based on the costs provided by an Oncology expert and the numbers and the distribution of new breast cancer cases by stage and corresponding annual treatment costs in specialist care sector (pre-cancer stage not included), we calculated that the mean total treatment cost of a new case of BC is 33 216 MDL (1 668 Euro) with total treatment costs of new patients (on a yearly basis) with BC to be 34 605 487 MDL (1 730 274 Euro).

Screening programs usually lead to increased prevalence of breast cancer. One of the positive effects of BCS is shifting to lower stages the BC. If we take into account a theoretical downshifting by 10% of the stage of detection of BC after implementing BCS at national level, the overall yearly cost of treatment of new cases of BC could be reduced by almost 1,000,000 MDL. We need to take into account that the actual number of registered cases of BC can increase after the implementation of BCS at national level, generating more costs. Also, we may face the loss of QALYs and the costs of treating women with BC who could have lived without the diagnosis. In the future, after more data are gathered, it will be important to perform a more comprehensive economic evaluation that will take into account the abovementioned aspects, that possibly could include a cost-effectiveness analysis, but also to ascertain our preliminary cost estimates.

Ethics

There is a debate about how many lives are saved by breast screening and how many women are diagnosed with cancers that would not have become life threatening: some women who are screened will be diagnosed and treated for breast cancer that would never have otherwise caused them harm and other will receive a negative (all clear) mammogram results although the cancer is present (false negative). It is therefore an ethical dilemma that an intervention that initially is meant to cure is actually causing harms. It is also important to mention that every woman undergoing BCS is assured of confidentiality and signs an informed consent in which a health care provider educates a patient about the risks, benefits, and alternatives of a given procedure or intervention.

Due to geographical distribution of oncology related healthcare services in the Republic of Moldova, concentrated mainly in the capital city at the Oncology Institute, more distant regions and particular subpopulations are more vulnerable and likely to have less access to screening, especially women in their late 50's from rural areas.

BCS needs to protect the individual's right to decide about their health and needs to guarantee that the eligible women do not feel obliged to attend the program by any means. However, these women may experience unnecessary worry and distress. This is why it is important to give the women all required information so that they are able to make an informed choice whether to be screened or not.

Discussion

This document is a pilot HTA-report on the topic selected and approved by major national stakeholders in health (MHLSP, NAPH, Oncology Institute). This HTA pilot was the first experience for the Moldovan team in conducting such an assessment and writing a HTA report. The main objective was for the team to learn about how to conduct a HTA and to assess the effect of breast cancer screening in the Republic of Moldova.

In brief, we have summarized the evidence base and the results by outcome, as follows:

1. Breast cancer related mortality
    I. The age range 40-49 years: screening probably does not reduce breast cancer mortality (moderate certainty of evidence - GRADE ⊕⊕⊕◯);
    II. The age range 50-69 years: screening reduces breast cancer mortality (high certainty of evidence - GRADE ⊕⊕⊕⊕);
    III. The age range 70-74 years: screening reduces breast cancer mortality (high certainty of evidence - GRADE ⊕⊕⊕⊕).
2. All cause (other cause) mortality
    I. The age range 40-49 years: we do not know if screening affects other cause mortality (very low certainty of evidence - GRADE ⊕◯◯◯);
    II. The age range 50-69 years: BCS may not reduce other cause mortality (low certainty of evidence - GRADE ⊕⊕◯◯);
    III. The age range 70-74 years: BCS may not reduce other cause mortality (low certainty of evidence - GRADE ⊕⊕◯◯).

3. Overdiagnosis (woman perspective)
    I. The age range 40-49 years: overdiagnosis (woman perspective) probably occurs in 22.7% of examined cases (moderate certainty of evidence - GRADE ⊕⊕⊕◯);
    II. The age range 50-69 years and 70-74 years: overdiagnosis (woman perspective) probably occurs in 17.3% of examined cases (moderate certainty of evidence - GRADE ⊕⊕⊕◯).
4. Quality of life (inferred from psychological effects)
    I. Anxiety in screened women appears to not increase if the procedures are clear and transparent, and the results are presented to them in a clear way;
    II. For women who are recalled the levels of anxiety may rise and subsequently the quality of life diminish at least for the waiting period;
    III. Certainties of evidence were low - GRADE ⊕⊕◯◯for all age ranges.
5. False-positive related adverse effects
    I. An overall false-positive rate of 20% in women undergoing 10 biennial screening tests;
    II. A rate of 2% and 1% of all screening examinations resulted in needle biopsy among women without breast cancer (initial and subsequent screens, respectively);
    III. A number of 0.19% and 0.07% of all screening examinations resulted in surgical interventions among women without breast cancer (initial and subsequent screens, respectively);
    IV. Certainty of these estimates were very low – GRADE ⊕◯◯◯.

Recommendations provided in the EU guidelines

For asymptomatic women with an average risk of breast cancer the ECIBC's Guidelines Development Group (GDG), based in the evidence reviewed and considering the balance of benefits to harms, the use of resource and participants' values and preferences, formulated the following recommendations:

- For women aged 40 to 44, suggests not implementing mammography screening (conditional recommendation, moderate certainty in the evidence);
- For women aged 45 to 49, suggests mammography screening over no mammography screening, in the context of an organised screening programme (conditional recommendation, moderate certainty in the evidence);
- For women aged 50 to 69, recommends mammography screening over no mammography screening, in the context of an organised screening programme (strong recommendation, moderate certainty in the evidence);
- For women aged 70 to 74, suggests mammography screening over no mammography screening, in the context of an organised screening programme (conditional recommendation, moderate certainty in the evidence).

Limitations and strengths of this HTA

In this assessment we decided to include only publications written in English. Although we did find various information, studies and articles written in Romanian and Russian

language, they all referred to already published studies in English in the databases we searched in.

Since the breast cancer screening program (BCSP) in Moldova has been established only recently, the document has some limitations in health economic model assumptions based on limited number of cases accumulated and variable modifications in costs that can occur during the ongoing BCSP: some unit and procedure costs are estimated and others are based on oncology expert's opinion, thus the costs could have been over or underestimatedIt will be worthwhile carrying out more in-depth economic evaluations and a primary cost analysis when the program has been going on for some more years. This will enable to understand the full costs of screening and treatment of patients with BC.

The NAPH team has benefited from technical assistance and support from the expert team (NIPH). Final draft report was assessed independently by two HTA experts from NIPH (technical review and professional review) which strengthens the validity of findings and conclusions provided in this report.

Screening of women < 50 years

There is a debate about whether BCS should be extended to younger women (i.e., 40-49 years). The National Clinic Protocol "Cancerul glandei mamare" PCN 102 and the National Control of Cancer Program for 2016-2025 define the criteria in which breast cancer screening could be recommended to women younger than 50 years and state the specific reasons when BCS should not be performed.

Updating this HTA

When updating this report, a more comprehensive evaluation of ethical, organizational aspects, patient perspective and a full economic evaluation related to BCS should be done. More information is required about sub-populations and demographic issues specific to national context in the Republic of Moldova (e.g. high rate of population living abroad, but with local residence).

Monitoring and collecting data on resource use and costs is warranted to provide more in depth evidence, including information on the population receiving BCS and outcomes will be important to provide more in depth evidence on the effect of BCS in Moldova, and ultimately to be able to tailor a screening program that is the best suited for our country.

Due to continuous changes in the demography and thus practices that would affect BCS in our country we advise this report to be updated no sooner than five years after this initial assessment. This will enable us to gather more information on the outcomes of BCS in the Republic of Moldova and is likely to influence/affect the preliminary cost estimates.

Authors' statement

This HTA pilot was the first experience for the Moldovan team in conducting such an assessment and writing a HTA report. Despite the ongoing Covid-19 pandemic that generated some delay in planned activities, we believe this report to be of high quality. Besides the aim to assess and review evidence and perform a cost evaluation of BCS in the Republic of Moldova, the main objective was for the team to learn about how to conduct a HTA.

Abbreviations

[Term]	[Definition]
AE	Adverse Event
BC	Breast cancer
BCS	Breast cancer screening
BCSP	Breast Cancer Screening Program
BI-RADS	Breast Imaging - Reporting and Database System
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CT	Controlled trial
CUA	Cost-utility analyses
ECIBC	The European Commission Initiative on Breast Cancer
EUnetHTA	European Network for Health Technology Assessment
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
GDP	Gross Domestic Product
HTA	Health technology assessment
INAHTA	The International Network of Agencies for Health Technology Assessment
JRC	The Joint Research Centre
QALYs	Quality-adjusted life years
QA	Quality assurance
MDL	Moldovan Leu
MoU	Memorandum of understanding
MeSH	Medical Subject Headings
MHLSP	Ministry of Health, Labor and Social Protection of the Republic

	of Moldova
MRI	Magnetic Resonance Imaging
NCR	National Cancer Registry
NR	Not reported
NPHA	National Public Health Agency
NIPH	Norwegian Institute of Public Health
PICOS	Population-Intervention-Comparator-Outcome-Study
PRO	Patient related outcomes
RCT	Randomized controlled trials
RR	Relative Risk
SoF	Summary of Findings
SR	Systematic review
USPSTF	The United States Preventive Services Task Force
USG	Ultrasound examination
WHO	World Health Organization

Preface

A Memorandum of understanding (MoU) between the Ministry of Health and Care Services of Norway and the Ministry of Health, Labor and Social Protection of the Republic of Moldova (MHLSP) on the cooperation in the field of health and medical sciences was signed in Geneva the 19th of May 2014. The following year the parties agreed on a Programme of Work for the years 2015-2017, signed the 13th of February 2015. Later, the National Public Health Agency (NPHA), the Norwegian Institute of Public Health (NIPH) and the World Health Organization Regional Office for Europe (WHO), signed a memorandum of understanding on the cooperation in the field of public health, that remains in effect until the 1st of January 2021. Under the tripartite agreement, the use of evidence for public health policy was identified as one of the areas in the institutional collaboration, including systematic reviews and health technology assessment (HTA). The collaboration acknowledges the work and standards developed by all parties, especially WHO which was fundamental to establish the initial key contacts between the parties to facilitate further collaboration.

As for today, there is no HTA unit institutionalized in the Republic of Moldova and only fragmented actions are underway in different governmental structures that can serve as basis for future work in the HTA field. The introduction of systematic reviews and HTA as a tool assessing public health interventions was provided through an initial two-day's workshop at NPHA in Chisinau, Moldova in September 2018. A follow-up two-day workshop was organized in November 2018 to present the use of HTA in decision-making and HTA's relevance in the Moldovan health care setting. Subsequently a core HTA working group was formed in the beginning of 2019 at NPHA, with the aim to develop capacities in Moldova through a pilot project with technical assistance from NIPH. A pilot HTA was initiated by NPHA on the topic selected by the MHLSP:"Effects of breast cancer screening in the Republic of Moldova". The working collaboration between the two national public health agencies has led to the completion of this deliverable, in December 2020 (Appendix 1).

Conflict of interest declaration

The members of the two working groups did not receive external funding, and they claim no conflict of interest. The members of the two working groups including project collaborators and experts involved in writing the report are solely responsible for the content.

Acknowledgement

The team expresses gratitude to the reviewers and to those who have contributed to the report, but are not co-authors. From NPHA, Health Economist Valeriu Doronin and from NIPH, Health Economist Anna Lien Espeland, Heupink Lieke Fleur and Chola Lumbwe provided precious feedback on the draft.

Introduction

Definitions and brief introduction to HTA

Health Technology Assessment (HTA) is defined by the International Network for Agencies for HTA (INAHTA) as a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle. The purpose is to inform decision-making in order to promote an equitable, efficient, and high-quality health system (1). The WHO defines HTA as the systematic evaluation of properties, effects and/or impacts of health technologies and interventions. It covers both the direct, intended consequences of technologies and interventions and their indirect, unintended consequences (2). The European Network for HTA (EUnetHTA) definition of HTA states that HTA is a multidisciplinary process that summarizes information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner (3). Its aim is to inform the formulation of safe, effective, health policies that are patient focused and seek to achieve best value. All three definitions concur, but emphasize slightly differently the various aspects of HTA.

Preparing a HTA is complex and involves many judgments. It is important that the methods used are validated and agreed upon prior to the assessment is performed. This should be done in a separate protocol. Performing a HTA involves: the a priori specification of a research question (defining the so-called PICO – Population, Intervention, Comparator, Outcome), clarity on the scope of the review and which studies are eligible for inclusion (based on defined PICO); making every effort to find all relevant research studies through systematic literature search from all relevant sources, and to ensure that issues of bias in included studies are accounted for; and analyzing the included studies in order to draw conclusions based on all the identified evidence in an impartial and objective way (4).

Further it is usual for systematic review to evaluate the included studies for risk of bias or quality. This information may be used in addition to similarity in participants, interventions, comparisons and outcomes in the decision as to whether effect estimates from several trials can be combined statistically in a meta-analysis. The risk of bias or quality should be used along the effect estimates when a conclusion is made in a systematic review (4).

Purpose of HTA

HTA was developed out of a need to ensure that decisions affecting people's lives can be informed by an up-to-date and complete understanding of the relevant research evidence. With the volume of research literature growing at an ever-increasing rate, it is impossible for individual decision makers to assess this vast quantity of primary research to enable them to make the most appropriate healthcare decisions that do more good than harm. By systematically assessing this primary research, systematic reviews aim to provide an up-to-date summary of the state of research knowledge on an intervention, diagnostic test, prognostic factor or other health or healthcare topic. Systematic reviews address the main problem with ad hoc searching and selection of research, namely that of risk of bias; just as primary research studies use methods to avoid bias, so should summaries and syntheses of that research (4).

Health technology assessment (HTA) refers to the systematic evaluation of properties, effects, and/or impacts of health technology. It is a multidisciplinary process to evaluate the social, economic, organizational and ethical issues of a health intervention or health technology.

HTA can be used in many ways to advise or inform technology-related policies and decisions (5). Among these are to advise or inform:

- Regulatory agencies about whether to permit the commercial use (e.g., marketing) of a drug, device or other regulated technology;
- Payers (health care authorities, health plans, drug formularies, employers, etc.) about technology coverage (whether or not to pay), coding (assigning proper codes to enable reimbursement), and reimbursement (how much to pay);
- Clinicians and patients about the appropriate use of health care interventions for a particular patient's clinical needs and circumstances;
- Health professional associations about the role of a technology in clinical protocols or practice guidelines;
- Hospitals, health care networks, group purchasing organizations, and other health care organizations about decisions regarding technology acquisition and management;
- Standards-setting organizations for health technology and health care delivery regarding the manufacture, performance, appropriate use, and other aspects of health care technologies;
- Government health department officials about undertaking public health programs (e.g., immunization, screening, and environmental protection programs);
- Lawmakers and other political leaders about policies concerning technological innovation, research and development, regulation, payment and delivery of health care;
- Health care technology companies about product development and marketing decisions;
- Investors and companies concerning venture capital funding, acquisitions and divestitures, and other transactions concerning health care product and service companies;
- Research agencies about evidence gaps and unmet health needs.

Breast cancer at global level and in the Republic of Moldova

Breast cancer is the most commonly occurring cancer in women and the second most common cancer overall with over 2 million new cases registered worldwide in 2018: in USA, breast cancer is the most frequent tumor in women with more than 3.5 million women with BC registered; in European Union, more than 500.000 new cases of BC are added on a yearly basis; in Romania, more than 3.500 death caused by BC are registered each year; in Ukraine, more than 6.500 new cases are diagnosed each year (6).

According to L.S. with personal access to National Cancer Registry (NCR) data from the Oncology Institute of the Republic of Moldova, in 2019 BC was the first cause of morbidity by cancer in women and represented 11.6% from yearly oncologic morbidity: in December 2019 there were more than 10000 registered patients in the NCR and more than 1000 were added in 2019 alone; women aged 50 and more during and after menopause is the most affected population with median age of the patients with BC in the Republic of Moldova of 59,0 years (Table 1) (7).

Table 1 Women diagnosed with BC by age (2015-2019)

Year	Age group (years)											
	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80+
2015	2	23	40	55	93	117	187	186	134	92	74	-
2016	4	23	47	65	112	147	187	218	175	81	97	-
2017	4	26	47	60	103	118	180	181	190	96	100	-
2018	4	18	34	57	87	101	163	184	211	131	69	41
2019	3	10	40	63	101	114	129	198	212	163	67	45
Total	**17**	**100**	**208**	**300**	**496**	**597**	**846**	**967**	**922**	**563**	**407**	**86**
Total (%)	**0.3**	**1.8**	**3.7**	**5.4**	**9.2**	**10.8**	**15.4**	**17.6**	**16.8**	**10.2**	**7.3**	**1.5**

According to the latest data provided by NCR at the Oncology Institute, the incidence of malign tumors of the breast is rising on a yearly basis: it is assumed that 1 in 9 women during her lifespan will acquire breast cancer. In 2015, 1013 new cases of breast cancer were detected (53.6 per mille and in 2017 the number grew to 1199 (65.0 per mille). In the same period of time, the morbidity by malign tumors of breast grew from 10.7% in 2015 to 11.9% in 2017 (7). Data for 2019 show that more than 32, 5% of women diagnosed with BC in 2019 were in stages III-IV (in 2015 – 42.7%, in 2017 – 43.7%), and 509 women died from BC in 2019 (Table 2).

Table 2 Women diagnosed with BC by stage (2015-2019)

Year	Total new cases	St. I	St. II	St.III	St. IV	Patients at the end of the year	During the first 5 years from detec-tion	Died during the first year after detec-tion
2015	923	123	477	149	174	9616	4405	73
2016	1143	133	624	258	128	8756	4533	133
2017	1102	149	567	278	108	9137	4757	112
2018	1085	122	582	283	98	9627	4976	126
2019	1151	169	600	254	128	10.074	5372	151
Total	**5404**	**696**	**2850**	**1222**	**636**			**483**
Total (%)	**100**	**12.9**	**52.7**	**22.6**	**11.8**			

It is very difficult to evaluate the economic burden of breast cancer in the Republic of Moldova: not all cases are diagnosed, most patients with BC are in late stages of the disease and the impact on the quality of life and work is not trully studied and counted. Overall, the financial and economic impact of breast cancer are not well understood and evaluated.

International recommendations on breast cancer screening

According to the Centers for Disease Control and Prevention's definition of Breast Cancer Screening, it means checking a woman's breasts for cancer before there are signs or symptoms of the disease (8).

The United States Preventive Services Task Force recommends that women who are 50 to 74 years old and are at average risk for breast cancer get a mammogram every two years. Women who are 40 to 49 years old should talk to their doctor or other health care professional about when to start and how often to get a mammogram. Women should weigh the benefits and risks of screening tests when deciding whether to begin getting mammograms before age 50 (8).

The National Health Service in the United Kingdom (NHS) states that all women aged from 50 to their 71st birthday who are registered with a GP are automatically invited for breast cancer screening every 3 years (9). Screening does not prevent you getting breast cancer, and it may not help if you already have advanced stage breast cancer. Breast screening helps identify breast cancer early. The earlier the condition is found, the better the chances of surviving it. According to NHS, risks of breast screening are overtreatment (women diagnosed and treated for BC that would never have otherwise caused them harm), unnecessary distress, missed diagnosis (1 in 2500 women screened in UK), radiation (during a mammogram, the breasts are exposed to a small

amount of radiation – 0,4 milisieverts). But the benefits of screening and early detection are thought to outweigh the risks of having the X-ray.

Breast cancer screening in the Republic of Moldova

Breast cancer screening (BCS) in Moldova started in October 2018 with the purchase of 4 mobile units with digital mammography, training of the professionals to lead the teams involved in the BCS and with MHLSP official document elaborated and published that describes all related procedures (10). Today, BCS is performed by 4 mobile units with digital mammography: during 1 working week the mobile unit is sent to different national districts according to the Ministry of Health, Labor and Social Protection strategy and approved timeline. Each mobile unit has a driver and a radiology expert, but does not include a doctor. All costs related to the maintenance of the mobile units (fuel, technical maintenance, parts and repairs) and personell costs are covered by the Oncolocy Institute and these costs are yearly covered by the National Health Insurrance Company. It is worth mentioning that every women has the right to perform a mammography at the nearest health institution, but the screening performed by mobile units remains the first choice for most women (based on age-bracket eligibility criteria) (10).

According to the national plan, each general practitioner in the screened district inform by phone women in the targeted population (women in the 40-65 age bracket) about the possibility of performing a BCS at a specific date and place (no financial incentives or other funds allocated for the invitation process). After 1 week of working in the district, the mobile unit returns to the Oncology Institute and passes all digital mammographies performed to two Oncology experts, that independently review the images and produce the final imaging report.

If an image may indicate BC or a woman is diagnosed with cancer or pre-cancerous disease (BIRADS III, IV, V) (Appendix 2), the patient is invited to the Oncology Institute for further examination using breast ultrasound examination (USG) and clinical examination by an onco-mammology expert. If a localized formation is suspected, a echoed diagnostic puncture is performed. Afterwards, a treatment is prescribed and often surgical treatment is recommended.

If breast USG and clinical examination by the onco-mammology expert (all performed at the Oncology Institute only) does not reveal any signs of BC, the patient is required to perform two more examinations by the onco-mammology expert: one after 3 months and the second after 6 months. If after two repeated examinations there are no signs of BC, the patient is removed from the list of suspected cases.

Method

Literature search

Based on the topic proposed for HTA by the Ministry of Health, Labor and Social Protection of the Republic of Moldova the HTA team determined the research question using the so-called PICOS (Population-Intervention-Comparator-Outcome-Study) design which was basis for the inclusion criteria (Table 3). The HTA Core Group determined the PICO question in collaboration with the NIPH team. Then the research librarian from NPHA (M.G.) elaborated the literature search strategy in collaboration with the HTA core group and with assistance from an information specialist from NIPH (MH). Search strategies were developed for the databases Epistemonikos, PubMed and the Cochrane Database of Systematic Reviews (Appendix 3). In addition, search for international guidelines (and SRs therein) were carried out in different electronic databases and websites as shown in Appendix 4.

We performed the search for studies between the 1st and the 15th of September 2019, while we searched for international guidelines between the 15th and the 30th of January 2020. We only included articles and guidelines in English language from 2016-2019 period.

Table 3 Inclusion criteria for relevant hits obtained from the search strategy

Population:	Asymptomatic women aged 40-75
Intervention:	Imaging technology: mammography (including 3D), MR, Ultrasound
Comparison:	No screening
Outcome:	All cause mortality, Breast cancer-related mortality, HRQoL, Harms (false positives or true positives, but treated without increased survival) including anxiety, overdiagnosis, and overtreatment.
Study design:	Systematic reviews (SR) and health technology assessments (HTA) Randomized controlled trials (RCT) if no SR/HTA of high quality
Language:	No limitations*

*Although no limitation for languages was included in the search, we decided to only include articles in English and articles with English abstract.

Selection of articles

Based on recommendations from research librarians (M.G. and M.H.) the team decided to use the PRISMA tool to illustrate the workflow of identification of documentation. At least two reviewers were to assess abstracts and potentially relevant full text publications independently. Disagreements were resolved through discussion to obtain consensus or by consulting a third party. It was decided that the most recent SRs (including SRs in guidelines) of highest quality (using the AMSTAR-2 tool) (11) relevant to the inclusion criteria should be included in our HTA.

Data extraction, analysis and grading the certainty of evidence of evidence

The two reviewers separately extracted the data from the included SRs (including SRs in guidelines) and checked that data was extracted correctly. Disagreements were resolved through discussion to obtain consensus or by consulting a third party. In case we had included primary studies and performed our own meta-analyses we planned to assess the quality of evidence using the GRADE instrument (Grading of Recommendations Assessment, Development, and Evaluation, www.gradeworkinggroup.org). The GRADE evaluation takes into account study limitations, inconsistency between trials, indirectness (in how similar the population, intervention, and outcomes are between the trials and the objectives of this report), imprecision of the estimates and publication bias. Finally the overall quality or certainty of evidence was categorized as high, moderate, low or very low.

GRADE categorizes the certainty of evidence into four levels:

Grade	Definition
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

Health economic evaluation

Economic evaluations of breast cancer screening are often carried out as cost-utility analyses (CUA). In such analyses, effectiveness is measured in terms of quality-adjusted life years (QALYs), i.e. years in good health. A screening programme is seen to be cost-effective if the cost per QALY gained (relative to no screening) is beneath an acceptable willingness to pay threshold (for example GDP per capita).

The team decided that based on the available information, two health economic experts (one from NIPH and one from NPHA), would estimate treatment costs and budget impact. Since the breast cancer screening programme (BCSP) in Moldova has been established only recently, the team recommend to carry out future economic evaluations, when the program has been going on for some more years.

General considerations about ethical implications

An ethical analysis in a HTA generally considers prevalent social and moral norms and values relevant to the technology in question. It involves an understanding of the consequences of implementing or not implementing a healthcare technology in two respects: with regard to the prevailing societal values and with regard to the norms and values that the technology itself constructs when it is put into use. This is to ensure that the assessments themselves are designed and conducted in such a way that key ethical principles are considered and respected. The issues stem from the general values of the population, aims of the healthcare system and values arising from the use of a technology (12).

The most important ethical aspects related to BCS will be briefly discussed. These include weighting the benefits against the risks of BCS, the importance of the informed consent and shared decision making between the health specialist and the person undergoing BCS, unequal access and possible inequities related to geography and demography.

Clinical effectiveness

Result of literature search

The selection of publication(s) is shown in the PRISMA chart in Figure 1. A total of 2365 records (604 from 3 databases and 1761 from international guidelines) were identified. After the duplicates were removed a total of 2047 records (393 from 3 databases and 1654 from international guidelines) were screened by two co-authors (L.B. and A.A.) independently. The search for guidelines resulted in 1761 hits, from which 107 were removed as duplicates. Further 1595 guidelines were excluded as not relevant to PICO for a total of 1970 records excluded based on not relevant to PICO (375 for SRs and 1595 for international guidelines). The potentially relevant 23 publications (18 for SRs and 5 guidelines) were assessed in full-text by three HTA group members (L.B., A.A. and S.O.). Relevant publications according to the predefined inclusion criteria were read in full text: 3 SRs and 5 guidelines (Appendix 5) were selected for further quality assessment by two HTA core group members (LB and SO), using the AMSTAR-2 tool (11) as shown in Appendix 7.

Of note, during the time of selection of articles, the team was informed that the new European guidelines had just been published. Therefore, the team decided to search for international guidelines on breast cancer screening that potentially could be based on SRs. We finally included the SRs from the newly published European guidelines from European Commission Initiative on Breast Cancer (ECIBC) (13). The quality assessment of these is shown in Appendix 8. We would like to point out that we have presented directly the GRADE assessments from these with no further quality checks. These are shown in the "Summary of Findings" tables in the results chapter of this report.

Table of the 22 excluded publications and reasons for exclusion are shown in Appendix 5. Of note, as this review process was initiated prior to the publication of the European Guidelines, the team had initially decided to include three SRs. These are shown in Appendix 5. Data extraction on 3 SRs selected is shown in Appendix 6 and the AMSTAR-2 assessment tool (11) on 3 SRs selected is shown in the Appendix 7.

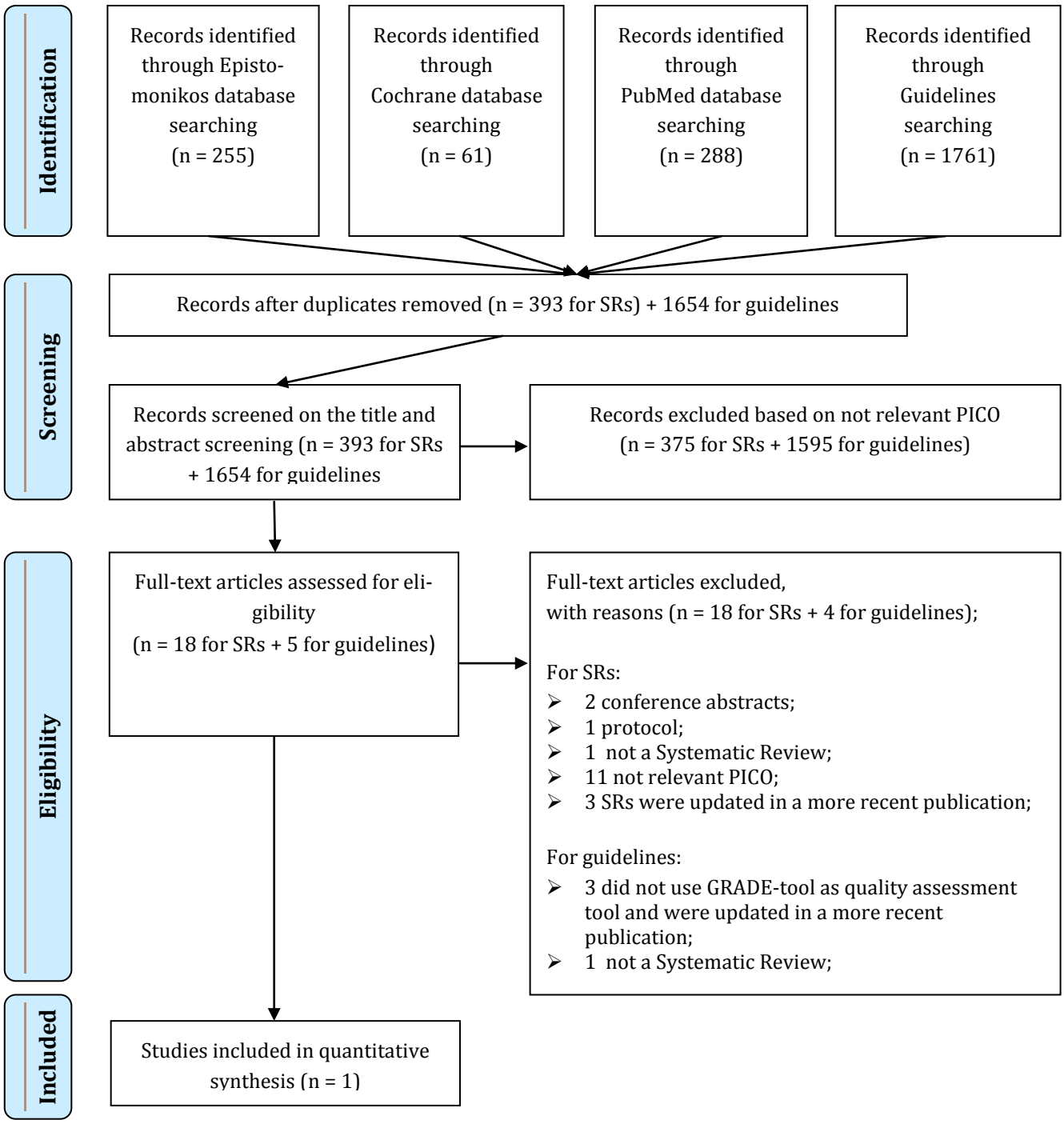

Figure 1 *Flowchart of identification of documentation (14).*

Description and assessment of the included evidence (systematic reviews) supporting the European (ECBIC) guidelines

European Commission Initiative on Breast Cancer (ECIBC)

The European guidelines on breast cancer screening and diagnosis and recommendation on mammography screening for women were developed by the Joint Research Centre (JRC) coordinated by the European Commission's Initiative on Breast Cancer (ECIBC). The ECBIC has two main tasks: 1) the development of a voluntary European quality assurance (QA) scheme for breast cancer services based on an EU legislative framework on accreditation covering all stages and aspects of care, and 2) the set-up of the evidence base for such a QA scheme via (i) the development of the new European guidelines for breast cancer screening and diagnosis and (ii) a platform for evidence-based breast cancer guidelines covering stages other than screening and diagnosis (e.g. rehabilitation, follow-up, psychological support and palliative care) (13).

Access to the ECBIC guidelines' supporting evidence (systematic reviews)

As no descriptions of the evidence (systematic reviews) the European guidelines are based on are yet publicly available, the NIPH team contacted JRC in September 2020 to request for the technical reports including the systematic reviews. NIPH received the draft document of the JRC technical report in October 2020 assessing whether mammography screening vs. no mammography screening should be used for detecting breast cancer in women produced by the JRC Science Hub of The European Union (https://ec.europa.eu/jrc). As the report is not yet published, it is not to be circulated and thus not included in this report.

Description of the supporting evidence (from the technical report developed for the ECBIC guidelines)

The technical report includes a systematic review of the evidence of the effects of mammography screening on breast cancer mortality and morbidity in women under the age of 50, 50-69 and 70 years and older. The authors followed standard Cochrane methods (15) and adhered to PRISMA guidelines for reporting systematic reviews (16). For the evaluation of the importance of the outcomes, the assessment of the certainty of the evidence and grading of recommendations the authors from JRC used the GRADE approach (17, 18).

The authors of the ECBIC guidelines performed the literature search in April 2016 in the databases MEDLINE, EMBASE and Central, which resulted in an initial set of 2393 unique citations. The authors of the technical report excluded 2377 citations (203 systematic reviews and 2174 individual studies) based on title or abstract assessment. They obtained 50 citations at full-text for detailed appraisal. After reviewing the full text they identified four systematic reviews of randomized controlled trials and two additional individual publications of RCTs published after the most recent systematic

review. All four systematic reviews identified the same eight RCTs of mammography screening. Of note, one of them, the SR by Nelson et al. (19) is the SR that was identified in our HTA, and was used by JRC collaborators as the main source of publications of the individual studies, because it is the most recent and comprehensive review, and it has included both RCTs and observational studies.

Based on all those sources and their search of individual studies, they finally included 25 publications from the eight RCTs, and three systematic reviews from observational studies that assessed the psychological and procedural impact of false positive results in the context of organized breast screening program (28 publications in total).

Assessment of the quality of the supporting evidence (systematic reviews supporting the ECBIC guidelines)

The quality of the SR on effect of BCS in the JRC technical report was assessed to be of high methodological quality using the AMSTAR-2 checklist (Appendix 8).

Effects of breast cancer screening

Mortality (breast cancer-related)

Eight RCTs including totally 152,344 screened women assessed the effect of BCS within the age range 40-49 years. Screening did not reduce breast cancer mortality as observed after a mean of 15.2 years of follow-up. The risks in the intervention and control groups were both 0.5% and RR was 0.92 with 95% CI ranging from 0.83 to 1.02. Certainty of the pooled estimates was moderate (⊕⊕⊕◯) according to the GRADE assessment (Table 4).

Six RCTs including in total 134,866 screened women assessed the effect of BCS within the age range 50-69 years. Screening reduced breast cancer mortality as observed after a mean of 15.5 years of follow-up. The risk in the intervention group was 0.5% versus 0.8% in the control group. The RR was 0.77 with 95% CI ranging from 0.67 to 0.88. Certainty of the pooled estimates was high (⊕⊕⊕⊕) according to the GRADE assessment (Table 4).

Two RCTs including 7,598 screened women assessed the effect of BCS within the age range 70-74 years. Screening reduced breast cancer mortality in the age groups 70-74 as observed after a mean of 20.0 years of follow-up. The risk in the intervention group was 0.8 % versus 0.9% in the control group. The RR was 0.77 with 95% CI ranging from 0.54 to 1.09. Certainty of the pooled estimates was high (⊕⊕⊕⊕) according to the GRADE assessment (Table 4).

Table 4: Summary of findings for breast cancer-related mortality

Age range	Nr of studies	Follow-up (mean years)	Organized mammography screening	No mammography screening	Relative effect (95% CI)	Absolute effect (95% CI)	Certainty of evidence (GRADE)
40-49	8 RCTs	15.2	736/152344 (0.5%)	0.5%	RR 0.92 (0.83 to 1.02)	38 fewer per 100,000 (from 82 fewer to 10 more)	⊕⊕⊕◯ MODERATE (*)
50-69	6 RCTs	15.5	740/134866 (0.5%)	0.8%	RR 0.77 (0.67 to 0.88)	175 fewer per 100,000 (from 251 fewer to 91 fewer)	⊕⊕⊕⊕ HIGH
70-74	2 RCTs	20.0	60/7598 (0.8%)	0.9%	RR 0.77 (0.54 to 1.09)	207 fewer per 100,000 (from 414 fewer to 81 more)	⊕⊕⊕⊕ HIGH

(*) Downgrading related to indirectness and imprecision

Mortality (other cause)

Six RCTs including totally 120,225 screened women assessed the effect of BCS within the age range 40-49 years. Screening did not reduce other cause mortality as observed after a mean of 10.8 years of follow-up. The risk in the intervention group was 2.8% versus 2.5% in the control group. The RR was 1.04 with 95% CI ranging from 0.95 to 1.15. Certainty of evidence in the pooled estimates was very low (⊕◯◯◯) according to the GRADE assessment (Table 5).

Three RCTs including totally 66,432 screened women assessed the effect of BCS within the age range 50-69 years. Screening did not reduce other cause mortality as observed after a mean of 9.6 years of follow-up. The risk in the intervention group was 6.7% versus 6.6% in the control group. The RR was 0.99 with 95% CI ranging from 0.95 to 1.04. Certainty of evidence in the pooled estimates was low (⊕⊕◯◯) according to the GRADE assessment (Table 5).

Two RCTs including totally 10,339 screened women assessed the effect of BCS within the age range 70-74 years. Screening did not reduce other cause mortality as observed after a mean of 7.9 years of follow-up. The risk in the intervention group was 27.4% versus 27.0% in the control group. The RR was 1.01 with 95% CI ranging from 0.91 to 1.10. Certainty of evidence in the pooled estimates was low (⊕⊕◯◯) according to the GRADE assessment (Table 5).

Table 5: Summary of findings for mortality (other cause)

Age range	Nr of studies	Follow-up (mean years)	Organized mammography screening	No mammography screening	Relative effect (95% CI)	Absolute effect (95% CI)	Certainty of evidence (GRADE)
40-49	6 RCTs	10.8	3349/120225 (2.8%)	2.5%	RR 1.04 (0.95 to 1.15)	100 more per 100,000 (from 125 fewer to 375 more)	⊕◯◯◯ VERY LOW (*)
50-69	3 RCTs	9.6	4479/66432 (6.7%)	6.6%	RR 0.99 (0.95 to 1.04)	66 fewer per 100,000 (from 330 fewer to 264 more)	⊕⊕◯◯ LOW (**)
70-74	2 RCTs	7.9	2834/10339 (27.4%)	27.0%	RR 1.01 (0.91 to 1.10)	270 more per 100,000 (from 2,430 fewer to 2,700 more)	⊕⊕◯◯ LOW (**)

(*) Downgrading related to inconsistency, indirectness and imprecision

(**) Downgraded due to indirectness and imprecision

Quality of life (inferred from psychological effects)

Anxiety in screened women appears to not increase if the procedures are clear and transparent, and the results are presented to them in a clear way (Table 6). For women who are recalled the levels of anxiety may rise and subsequently the quality of life diminish at least for the waiting period (Certainty of evidence low ⊕⊕◯◯for all age ranges).

Table 6: Summary of findings) for Quality of life (inferred from psychological effects)

Age range	Study (N)	Description of the studies conducted	Certainty of evidence (GRADE)
<50 50-69; 70-74.	54 observational studies	One systematic review with 54 studies included -no meta-analysis - (Brett 2005). Mammographic screening does not appear to create anxiety in women who are given a clear result after a mammogram and subsequently placed on routine recall. Mixed results about anxiety in women recalled for further testing: several studies reported transient or long term (from 6 months to 1 year after recall) anxiety, while other studies reported no differences in anxiety levels. The nature and extent of further testing seem to determine the extent of anxiety.	⊕⊕◯◯ LOW (*) (For all age ranges)

(*) Downgrading related to inconsistency, indirectness and imprecision

False-positive related adverse effects

Four observational studies assessed the false-positive effects on 390.000 screened women aged 50 to 69 with focus on biopsies and surgeries undertaken after BCS (Table 7). Results showed an overall false-positive screening results of 19.7% in women undergoing 10 biennial screening tests (pooled risk estimate based on 3 studies; range 8-21%). The results from EUNICE Project (20) (women aged 50 to 69) showed that 2.2% and 1.1% of all screening examinations resulted in needle biopsy among women without breast cancer (initial and subsequent screens, respectively). In addition, 0.19% and 0.07% of all screening examinations resulted in surgical interventions among women without breast cancer (initial and subsequent screens, respectively). Certainty of evidence in the estimates was very low (⊕◯◯◯) according to the GRADE assessment.

Table 7: Summary of findings) for false-positive related adverse effects (biopsies and surgeries)

Age range	Study (N)	Description of the studies conducted	Certainty of evidence (GRADE)
<50 50-69; 70-74.	4 observational studies	Results from 4 studies (390 000 women aged 50 to 69) showed an overall false-positive screening result of 19.7% in women undergoing 10 biennial screening tests (pooled risk estimate based on 3 studies; range 8 - 21%). This was related to a 2.9% pooled cumulative risk of an invasive procedure with benign outcome (range 1.8% to 6.3%; 2 studies) and 0.9% risk of undergoing surgical intervention with benign outcome (1 study) (21).	⊕◯◯◯ VERY LOW (*) (For all age ranges, except 50-69 age range, where

		Cross-sectional data from the EUNICE Project (women aged 50 to 69): 17 countries, 20 screening programs, 1.7 million initial screens, 5.9 million subsequent screens (20) showed that 2.2% and 1.1% of all screening examinations resulted in needle biopsy among women without breast cancer (initial and subsequent screens, respectively). In addition, 0.19% and 0.07% of all screening examinations resulted in surgical interventions among women without breast cancer (initial and subsequent screens, respectively).	the certainty of evidence (GRADE) was designated as ⊕⊕◯◯LOW)

(*) Downgrading related to inconsistency, indirectness and imprecision

Twenty-four observational studies assessed the false-positive related adverse effects on screened women with focus on psychological distress after BCS (Table 8) with the certainty of evidence of the estimates very low (⊕◯◯◯) according to the GRADE assessment. The results of the studies show that women who received a false-positive mammogram result had greater distress, fear, anxiety, and worry about breast cancer.

Table 8: Summary of findings for false-positive related adverse effects (psychological distress)

Age range	Study (N)	Description of the studies conducted	Certainty of evidence (GRADE)
<50 50-69; 70-74.	24 observational studies	One review (17 studies) found that women who received a false-positive mammogram result had greater distress, fear, anxiety, and worry about breast cancer (Saltz 2010). The second review (7 studies) showed that the psychological distress using diseases-specific measurements, in women (age not specified) with a false-positive mammogram at 35 months after the last assessment was: for women that needed further mammography RR=1.28 (95%CI 0.82-2.00); for women placed in early recall the RR=1.82 (95%CI 1.22-2.72); for women that needed a fine needle puncture aspiration RR=1.80 (95%CI 1.17-2.77); for women that needed a biopsy RR=2.07 (95%CI 1.22-3.52); no differences in generic measures of general anxiety and depression were observed at 6 weeks after assessment and 3 months after screening (Bond, 2013).	⊕⊕◯◯ LOW

Overdiagnosis (woman perspective)

Overdiagnosis (woman perspective) occurred in 22.7% of examined cases (95% CI 18.4%-27.0%) in the age group 40-49 (1 RCT and 1 observational study). Certainty of evidence in the pooled estimate was moderate (⊕⊕⊕◯) according to the GRADE assessment (Table 9). Overdiagnosis (woman perspective) occurred in 17.3% of examined cases (95% CI 14.7%-20.0%) in the age groups 50-69 (2 RCTs) and 70-74 (2 RCTs). Certainty of evidence in the pooled estimates was moderate (⊕⊕⊕◯) according to the GRADE assessment (Table 9). As a result of these studies, an excess of cancers were diagnosed during the screening period in women invited for screening (woman perspective).

Table 9: Summary of findings for overdiagnosis (woman perspective)

Age range	Study (N)	Description of the studies conducted		Certainty of evidence (GRADE)
40-49	1 RCT and 1 observational study	22.7% (95% CI 18.4%-27.0%)	Overdiagnosis calculated from CNBSS-1 trial, in which women in the control group were not offered mammography screening at the end of the trial. Excess cancers as a proportion of cancers diagnosed during screening period in women invited for screening (woman perspective).	⊕⊕⊕◯ MODERATE
50-74	2 RCTs	17.3% (95%CI 14.7%-20.0%)	Estimate from a meta-analysis of 2 trials (CNBSS-2 and Malmo I) in which women in the control group were not offered mammography screening at the end of the trial. Excess cancers as a proportion of cancers diagnosed during screening period in women invited for screening (woman perspective).	⊕⊕⊕◯ MODERATE

Budget impact of performing BCS in the Republic of Moldova

Epidemiology of breast cancer in the Republic of Moldova

Breast cancer accounts for 17% of the total number of cancer cases in the country, the incidence in 2019 was 1151 new cases and the prevalence is approximately 10 000 patients in a population of 2.6 million, of which 1.404.555 are women (Table 10) (7).

Table 10: Major demographic indicators for Republic of Moldova (22)

2019	Overall	Men	Women
Population	**2.681.734**	1.277.180	1.404.555
Percentage	**100%**	47.62%	52.38%

Breast Cancer Screening Program in the Republic of Moldova started the 15th October 2018 and aimed for screening asymptomatic women in the 40-65 age brackets (493.789 women). In the 15.10.2018 - 31.12.2019 period of time, a total of 18109 mammograms were performed in the 40-65 age brackets, including recalls (16% of all mammograms already performed).

Costs of BCS in the Republic of Moldova

Based on official data on prices per procedure (7), Table 11 below shows the variable costs of screening given the input provided. The costs of the mammogram and the recall (i.e. second reading) are assumed to be identical and include direct (personnel costs) and indirect (consumables) costs. Total costs per 18 109 mammograms performed until 31.12.2019 (including 16% of recalls) were 5.668.117 MDL (283.406 Euro).

Table 11: Costs of breast cancer screening

	MDL	Euro*
Cost per mammogram	313	15.65
Cost of purchase of 1 mobile unit used for BCS	468 000	23 400
***Costs of operating the mobile unit**	N/A	N/A
****Direct personnel costs**	N/A	N/A

*All costs related to day-to-day use of the mobile buses involved on a permanent basis in BCS are covered by the Oncology Institute and are granted by the National Insurance in Health Company under the rules of a bilateral contract signed yearly.
**All health personnel that are involved on a permanent basis in BCS activities do not receive additional financial incentives besides the salary and financial remuneration that are covered by their main employee and are based on current national laws.

Total Cost of purchase of the 4 mobile units used for BCS was 1.872.000 MDL (93.600 euro) which will have to be amortized over the buses' lifetime to calculate the annual cost of screening. Based on health economist's recommendation (V.D.) we assume the amortization period for a mobile unit to be 10 years and the amortization costs for all 4 mobile units should be added to overall cost of screening (ca 187 200 MDL/9360 Euro/mobile unit/year*).

Costs of BC treatment in the Republic of Moldova

The annual treatment costs for new cases (including costs for outpatient consultations, chemotherapy/radiation and hospital admissions) is around 34.6 million MDL or 1.7 million euro* per year, with BC treatment costs accordingly to the stage of detection vary from around 650 euro/patient to almost 2500 euro/patient in stage III and IV (7). In addition to the costs associated with new cases, costs for breast cancer patients diagnosed in cohorts from previous years will also be incurred.

Table 12: Distribution of new breast cancer by stage and corresponding annual treatment costs in specialist case sector (pre-cancer stage not included)

Stage	**Number of cases**	**Treatment cost per case**		**Total treatment costs**	
		MDL	Euro*	MDL	Euro*
Stage I	165	13169	658	2 172 885	108 644
Stage II	586	24757	1237	14 507 602	725 380
Stage III	248	47800	2390	11 854 400	592 720
Stage IV	127	47800	2390	6 070 600	303 530
No stage	25	-	-	-	-
Sum	1151	-	-	34 605 487	1 730 274

*Estimated exchange rate: 1 Euro = 20.00 MDL

The mean treatment cost based on new cases of BC is 33216 MDL 1 668 Euro*. We cannot, however, extrapolate from incidence in order to estimate the total number of cases within each stage of BC since we do not know the distribution between breast cancer stages and some patients will probably be without treatment for a period of time.

If we assume a positive scenario of downshifting by 10% the stage of detection of BC after implementing BCS at national level by reducing 10% from stage III and IV and reallocate them to stage I and II, respectively, but keeping the overall number of cases the same, the overall yearly cost could be reduced by almost 1.000.000 MDL. A recommendation would be to perform a more depth economic evaluation on the topic in the future.

Sensitivity analysis

A screening program has the potential to generate QALYs. The cost per QALY will be lower if the costs of screening are offset to some degree by a reduction in total breast cancer treatment costs as a result of earlier detection.

Based on sensible data and description of processes provided by Oncology expert L.S. by using internal access to National Cancer Registry (NCR) and bilateral contract signed with the National Insurance in Health Company the cost per unit of one BCS procedure performed in the 15.10.2018 - 31.12.2019 period of time (cost per procedure + direct personnel costs + cost of operating the mobile unit + other indirect costs) was announced to be of 512 MDL (25.60 Euro). Based on available data we can calculate potential costs of performing BCS in the Republic of Moldova using the formula:

"Target population" X "Cost per unit"

If we assume that BCS will be performed by all women in the target population in the 40-65 age brackets (493.789 women) within the current costs, then total costs would rise to 255.819.968 MDL (12.640.998 Euro). If we assume that this will be completed within a 5 year timeframe this will generate costs of more than 50 million MDL (2.5 Million Euro) per year.

In the light of EU Guidelines recommendations, BCS in the Republic of Moldova could extend to cover a more vast women population of 626.733 women (40-75 age brackets) with an increase of more than 130.000 women compared to current target population. If we assume that BCS protocol in the Republic of Moldova will change in line with the EU Guidelines' recommendations (screening of women in the 40-75 age brackets) then the target population will rise to 626.733 women. Within the current costs, performing BCS to women in the 40-75 age brackets will need more than 320.887.296 MDL (16.044.364 Euro). If we assume that this will be completed within a 5 year timeframe this will generate costs of more than 60 million MDL (3 Million Euro) per year.

Organization

The organizational aspects of a health technology or intervention considers what kind of resources (material artifacts, human skills and knowledge, money, attitudes, work culture, etc) have to be mobilized and organized when implementing a new technology, and what kind of changes or consequences the use can further produce in the organization (23).

In the Republic of Moldova, Breast Cancer Screening started on 15 October 2018 (10). As agreed between the Ministry of Health, Labor and Social Protection (MHLSP), the Oncology Institute and State University of Medicine and Pharmacy "Nicolae Testemitanu", the National Program "Un doctor pentru tine" ("A doctor for you") included breast cancer screening.

As stated in the official decree of the MHLSP (10), a formal structure was established:

1) A National coordinator of BCS was chosen to be the Director of the Oncology Institute. He is responsible for supervising the process of BCS at national level and reports two times a month to the MHLSP.
2) Regional coordinators are designated by the directors of the regional health institutions in the districts that will be offering BCS according to the national plan (10). They are responsible for the organization and coordination at local level, and report to the National Coordinator.
3) Four mobile units are currently operating in the BCS program, and include an imaging specialist (a radiographist), a medical registrar, a driver and a nurse.

The selection of eligible women for BCS is performed by the general practitioner from the district screened (24). All women with age between 40 and 65, asymptomatic at the time of screening are proposed to perform BCS within a time frame of two years. Women with existing preconditions (severe decompensate diseases) are excluded from BCS. Based on the time schedule proposed by the MHLSP, local authorities select all eligible patients for performing BCS in the selected region. General practitioners and family doctors in the region prepare the list of eligible women to perform BCS and invite them at a specific date and time in a specific place in town. The mobile unit stay located in the same region for 5 days during the working week and performs digital mammography to all women on the list who attends the mobile unit.

All screened women sign an informed consent before the procedure and receive a unique registration number upon completion – a BI-RADS code (Breast Imaging - Reporting and Database System) (Appendix 2), a common international practice for coding mammography, ultrasound examination and MRI results. The code offers a risk score used for further diagnostic and treatment of BC cases. All imaging results are digitally stored in the mobile unit and transmitted to a doctor (oncologist mammologist) at the Oncology Institute for examination. All suspected imaging results are independently reviewed by two oncology experts. The results are disseminated to patients through official communication channels.

Based upon already gained experience and the available mobile units, oncology experts have suggested to continue BCS using the existing methodology, thus assuring that digital mammography will be available in rural areas located far from cities and that BCS will be granted for vulnerable subgroups, older population and persons with no possibilities for traveling to the Oncology Institute in the capital city.

Ethical implications

Weighting the balance between benefits and the risks of BCS is challenging

There is a debate about how many lives are saved by breast screening and how many women are diagnosed with cancers that would not have become life threatening. For instance, in the UK, screening saves about 1 life from breast cancer for every 200 mammograms performed (25). About 3 in every 200 women screened every 3 years from the age of 50 to 70 are diagnosed with a cancer that would never have been found without screening, and would never have become life threatening (25), adds up to about 4,000 women each year in the UK who are offered treatment they did not need. Overall, for every 1 woman who has her life saved from breast cancer, about 3 women are diagnosed with a cancer that would never have become life threatening (in other words, some women who are screened will be diagnosed and treated for breast cancer that would never have otherwise caused them harm) (25). On the other hand, there is a small chance that a woman will receive a negative (all clear) mammogram results although the cancer is present (false negative). Breast screening picks up most breast cancers, but it misses breast cancer in about 1 in 2,500 women screened. It is therefore an ethical dilemma that an intervention that initially is meant to cure is actually causing harms.

Following screening, about 1 in 25 women will be called back for further assessment (25). Reasons for the recall are often due to technical issues or that the first mammogram may have been unclear and thus difficult to analyze. Most of these cases are found to be cancer free when screened a second time. However, these women may experience unnecessary worry and distress. About 1 in 4 women who are called back for further assessment are diagnosed with breast cancer (25).

A mammogram is a type of X-ray, and X-rays may, very rarely cause cancer, but is considered safe for women only being exposed a few times. During a mammogram, breasts are exposed to a small amount of radiation (25). For comparison, in the UK, a person receives a dose of 2.2 mSv a year from natural background radiation. However, the benefits of screening and early detection are thought to outweigh the risks of having the X-ray.

Informed consent /shared decision making

It is also important to mention that every woman undergoing BCS is assured of confidentiality and signs an informed consent (26) in which a health care provider educates a patient about the risks, benefits, and alternatives of a given procedure or intervention. The patient must be competent to make a voluntary decision about whether to undergo the procedure or intervention. Informed consent is both an ethical and legal obligation of medical practitioners and originates from the patient's right to direct what happens to their body. Implicit in providing informed consent is an assessment of the patient's understanding, rendering an actual recommendation, and documentation of the process.

Unequal access (or inequities related to geography and demography)

Due to geographical distribution of oncology related healthcare services in the Republic of Moldova, concentrated mainly in the capital city at the Oncology Institute, more distant regions and particular subpopulations are more vulnerable and likely to have less access to screening, especially women in their late 50's from rural areas. This creates an ethical problem of geographical and demographic inequity that need to be taken into consideration by the MHLSP.

Overall, having a national BCS Program in place benefits the whole female population of the Republic of Moldova and will have long term positive effects on human dignity and equity. In any circumstances, BCS needs to protect the individual right to decide about their health and needs to guarantee that the eligible women do not feel obliged to attend the program by any means.

Patient perspectives and ethical implications

Awareness of how valuable patients' perspectives are within healthcare services grew in the 1970s with a WHO declaration stipulating that health is not defined solely by absence of disease, but also includes physical, physiological and social wellbeing of the individual. The term individual is sometimes used synonymously with 'patient', but it can also refer to a healthy individual, who receives health technologies, e.g. a person taking part in a screening program.

There may be some social groups that are particularly important to consider for a specific health technology or for which there is a policy imperative for special consideration (such as those with disabilities) or in which the value of the technology may be different (such as ethnic minorities) and these may need to be specified. Patients, caregivers and individuals will have a range of perspectives and an HTA should seek to gather as much evidence as possible to understand these wide ranging views.

It is important to mention that women have different thresholds for what is a benefit and what is a risk in regard of performing a BCS. This generates uncertainties regarding expected benefits and expected harms for the overall target population and what is the "right" balance between them.

The team acknowledges the importance of assessing ethical implications in HTAs and especially with regard to interventions such as breast cancer screening. However, due to time constraints and limited resources available to carry out this HTA, we recommend having a separate study on ethical issues related to breast cancer screening.

Discussion

SUMMARY OF MAIN RESULTS

This document is a pilot HTA-report on the topic selected and approved by major national stakeholders in health (MHLSP, NAPH, Oncology Institute. To assess the effect of breast cancer screening we have summarized the evidence base from the current European guidelines. In brief, the results are the following:

Breast cancer related mortality

- Eight RCTs including totally 152,344 screened women assessed the effect of BCS within the age range 40-49 years. Screening did not reduce breast cancer mortality as observed after a mean of 15.2 years of follow-up. RR=0.92 (95% CI 0.83-1.02) with moderate certainty of evidence (GRADE ⊕⊕⊕◯).

- Six RCTs including in total 134,866 screened women assessed the effect of BCS within the age range 50-69 years. Screening reduced breast cancer mortality as observed after a mean of 15.5 years of follow-up. RR=0.77 (95% CI 0.67-0.88 with high certaintyof evidence (GRADE ⊕⊕⊕⊕).

- Two RCTs including 7,598 screened women assessed the effect ov BCS within the age range 70-74 years. Screening reduced breast cancer mortality as observed after a mean of 20.0 years of follow-up. RR=0.77 (95% CI 0.54-1.09) with high certainty of evidence (GRADE ⊕⊕⊕⊕).

All cause (other cause) mortality

- Six RCTs including totally 120,225 screened women assessed the effect of BCS within the age range 40-49 years. Screening did not reduce other cause mortality as observed after a mean of 10.8 years of follow-up. RR=1.04 (95% CI 0.95 to 1.15) with very low certaintyof evidence (GRADE ⊕◯◯◯).

- Three RCTs including totally 66,432 screened women assessed the effect of BCS within the age range 50-69 years. Screening did not reduce other cause mortality as observed after a mean of 9.6 years. RR=0.99 (95% CI 0.95 to 1.04) with low certainty of evidence (GRADE⊕⊕◯◯).

- Two RCTs including totally 10,339 screened women assessed the effect of BCS within the age range 70-74 years. Screening did not reduce other cause mortality as observed after a mean of 7.9 years. RR=1.01 (95% CI 0.91 to 1.10) with low certainty of evidence (GRADE⊕⊕◯◯).

Overdiagnosis (woman perspective)

Overdiagnosis (woman perspective) occurred in 22.7% of examined cases (95% CI 18.4%-27.0%; 1 RCT and 1 observational study) in the age group 40-49 with moderate certainty of evidence (GRADE ⊕⊕⊕◯). Overdiagnosis (woman perspective) occurred in 17.3% of examined cases (95% CI 14.7%-20.0%; 2 RCTs) in the age group 50-69 and 70-74 with moderate certainty of evidence (GRADE ⊕⊕⊕◯). As a result of these studies, an excess of cancers were diagnosed during the screening period in women invited for screening (woman perspective).

Quality of life (inferred from psychological effects)

Anxiety in screened women appears to not increase if the procedures are clear and transparent, and the results are presented to them in a clear way. For women who are recalled the levels of anxiety may rise and subsequently the quality of life diminish at least for the waiting period (certainty of evidence low ⊕⊕◯◯ for all age ranges).

False-positive related adverse effects

Four observational studies assessed the false-positive effects on 390.000 screened women aged 50 to 69 with focus on biopsies and surgeries undertaken after BCS. Results showed an overall false-positive screening results of 19.7% in women undergoing 10 biennial screening tests (pooled risk estimate based on 3 studies; range 8-21%). The results from EUNICE Project (20) (women aged 50 to 69) showed that 2.2% and 1.1% of all screening examinations resulted in needle biopsy among women without breast cancer (initial and subsequent screens, respectively). In addition, 0.19% and 0.07% of all screening examinations resulted in surgical interventions among women without breast cancer (initial and subsequent screens, respectively). Certainty in the estimates was very low (⊕◯◯◯) according to the GRADE assessment.

Recommendations provided in the EU guidelines

For asymptomatic women with an average risk of breast cancer the ECIBC's Guidelines Development Group (GDG), based in the evidence reviewed and considering the balance of benefits to harms, the use of resource and participants' values and preferences, formulated the following recommendations:

- For women aged 40 to 44, suggests not implementing mammography screening (conditional recommendation, moderate certainty in the evidence);

- For women aged 45 to 49, suggests mammography screening over no mammography screening, in the context of an organised screening programme (conditional recommendation, moderate certainty in the evidence);
- For women aged 50 to 69, recommends mammography screening over no mammography screening, in the context of an organised screening programme (strong recommendation, moderate certainty in the evidence);
- For women aged 70 to 74, suggests mammography screening over no mammography screening, in the context of an organised screening programme (conditional recommendation, moderate certainty in the evidence

Screening of women < 50 years

There is a debate about whether BCS should be extended to younger women (i.e., 40-49 years). According to the National Clinic Protocol "Cancerul glandei mamare" PCN 102 and the National Control of Cancer Program for 2016-2025, BCS could be recommended to women younger than 50 years if one or more of the following are confirmed:

1. Family history of BC or genetic mutations at BRCA 1 or/and BRCA 2, TP 53 or PTEN genes;
2. Family history of hormone-dependent cancer;
3. Persons that went through radiotherapies at thoracic level for other disease;
4. Persons that have long time hormone-based therapies (including estrogens).
5. Persons that have not got a mammography for the last 2 years.

Women who should not have BCS

The PCN 102 and the National Control of Cancer Program for 2016-2025 also states that BCS should not be performed if one or more of the following are confirmed:

1. Persons after 70 years of age;
2. Persons that got a mammography in the last 2 years;
3. Patients with already confirmed BC;
4. Patients that do not want to have a mammogram;
5. Patients with severe decompensate diseases.

STRENGTHS AND WEAKNESSES OF REVIEW

In this assessment only publications written in English were decided to be included. Although we did find various information, studies and articles written in Romanian and Russian, they all referred to already published studies in English in the databases we searched in.

Second, during the time of selection of articles, the team was informed that the new European guidelines had just been published. Therefore, the team decided to search for international guidelines on breast cancer screening that potentially could be based on SRs. As we finally included the SRs from the newly published European guidelines (13) we decided to present the GRADE assessments already done in these.

Third, since the breast cancer screening program (BCSP) in Moldova has been established only recently, the document has some limitations in health economic model assumptions based on limited number of cases accumulated and variable modifications in costs that can occur during the ongoing BCSP. It will be worthwhile carrying out more in-depth economic evaluations when the program has been going on for some more years.

The NAPH team has benefited from technical assistance and support from the expert team (NIPH). Final draft report was assessed independently by two HTA experts from NIPH (technical review and professional review) which we believe strengthens the validity of findings and conclusions provided in this report.

IMPLICATIONS FOR PRACTICE AND RESEARCH

BCS in the Republic of Moldova started in October 2018, and no other evaluation of the procedures and policies related to BCS have been performed prior to this report. Therefore, monitoring and collecting data is warrant to provide more in depth evidence, including information on the population performing BCS and outcomes will be important to provide more in depth evidence on the effect of BCS in Moldova, and ultimately to be able to tailor a screening program that is the best suited for our country.

When updating this report, a more comprehensive evaluation of ethical, organizational aspects and patient perspective related to BCS should be included. More information is required about sub-populations and demographic issues specific to national context in the Republic of Moldova (e.g. high rate of population living abroad, but with local residence). Due to continuous changes in the demography and thus practices that would affect BCS in our country we advise this report to be updated no sooner than five years after this initial assessment. This will enable to gather more information on the outcomes of BCS in the Republic of Moldova and is likely to influence/affect the preliminary cost estimates.

Conclusion

Breast cancer is the most commonly occurring cancer in women and the second most common cancer overall with over 2 million new cases registered worldwide in 2018. In the Republic of Moldova, breast cancer accounts for 17% of the total number of cancer cases with more than 1000 new cases added each year for a prevalence of over 10 000 patients in a population of 2.6 million. Data show that more than 32.5% of women diagnosed with BC in 2019 were in stages III-IV. Based on health economic evaluation, total treatment costs for the 1,151 new cases of BC in 2019 could rise up to 34 605 487 MDL (1 730 274 Euro).

RCTs compared invitation to mammography screening with no invitation. Mammography screening reduced breast cancer mortality in women 50-69 years and 70-74 years (high certainty of evidence), but not in women <50 years (moderate certainty of evidence). The intervention had no significant effect in reducing other cause mortality in any age group (low certainty of evidence). There was evidence of increased harm among women randomized to invitation to screening on the following outcomes: overdiagnosis occurring (woman perspective), all ages (moderate certainty of evidence); increased levels of anxiety and lowered quality of life, all ages (low evidence); increased rates of false-positive related adverse effects, all ages (low certainty of evidence).

European Union Guidelines recommend implementing mammography screening over no mammography screening in the 50-69 age group (strong recommendation), suggest implementing mammography screening over no mammography screening in the 45-49 and 70-74 age groups (conditional recommendation) and suggest not implementing mammography screening in the 40-44 age group (conditional recommendation).

If we assume a positive scenario of downshifting by 10% the stage of detection of BC after implementing BCS at national level (by reducing 10% from stage III and IV and reallocate them to stage I and II, respectively), but keeping the overall number of cases the same, the overall yearly cost could be reduced by almost 1 000000 MDL. We could assume that the actual number of new BC detected in later stages will lower after the introduction and running of BCS (based on the informational campaigns, rise of women awareness and better management of the detected cases) that could lead to diminish considerably the actual costs incurred.

High certainty of evidence indicates overall benefits of screening in terms of preventing premature deaths due to breast cancer. The age range that has the maximum benefit from screening is 50-69 years. However, there remain some questions to be answered about overdiagnosis and false-positive related adverse effects, along with some more in-depth ethical considerations to be evaluated. Since breast cancer screening in the Republic of Moldova was only initiated in 2018, the benefit in terms of spared lives and cost savings will be seen in the longer term.

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Appendices

Appendix 1 Protocol for a systematic literature review (Project plan)

SUMMARY

Project category and commissioner	
Product (program area):	Systematic literature review
Thematic area:	Breast cancer screening in Republic of Moldova
Commissioner:	Ministry of Health, Labor and Social Protection of the Republic of Moldova
Project leader and review group	
Project manager:	Maria Cumpana, Deputy Director (NAPH, Republic of Moldova)
Responsible for the project:	Maria Cumpana, Deputy Director (NAPH, Republic of Moldova)
Internal project participants:	Liliana Buzdugan (NAPH, Republic of Moldova) Angela Anisei (NAPH, Republic of Moldova) Sergiu Otgon (NAPH, Republic of Moldova) Mariana Gore (NAPH, Republic of Moldova) Valeriu Doronin (NAPH, Republic of Moldova)
External project participants:	Larisa Sofroni (Oncology Institute, Republic of Moldova) Ingvil Von Mehren Sæterdal, Katrine Fronsdal, Steve Diaz French, Marita Heintz, Espen Movik (all from Norwegian Institute of Public Health)

OBJECTIVE

As for today, in Moldova there are two opinions on breast cancer screening: the first is to cover healthy women between 40 and 65 years and the second is aiming for targeting healthy women from 50 to 70 years. For every healthy women screened it is recommended to perform the mammography once in every 2 years, for a total of 10 mammographies during the 20 years. The question is therefore which of the two options are the best suited for Moldova realities. By performing a systematic review on the effect of breast cancer screening(BCS), we are aiming to obtain evidences for supporting the major national stakeholders in health to decide on which option to use in Moldova.

The purpose of this project is to answer the following issues:

The aim of this systematic review is to determine the clinical effects and effectiveness of breast cancer screening and find if there are differences in clinical outcomes in all age groups, including the abovementioned age groups: 40-65 and 50-70. By comparing screening using imaging techniques (X-ray mammography) with no screening, we will assess benefits in terms of mortality (both cancer-related and overall), quality of life, and potential harms, such as overdiagnosis and anxiety. In addition, we will assess costs consequences, by doing a health economic cost analysis.

BACKGROUND

At this point, breast cancer is the second cause of cancer related morbidity in the Republic of Moldova with 11,2% (1). Since 01.01.2019 to 31.12.2019, the national registry of patients with breast cancer ("National Cancer Registry") has included 10,169 women (2). Each year, more than 1000 new cases are discovered (22% of all cancer related diseases discovered per year), and 62% of them are stages I-II (in 2019, 1151 new breast cancer cases were reported: St. I –165 new cases; St. II - 586 new cases; St. III - 248 new cases; St. IV-127 new cases; No stage allocated -25 new cases) (1).

The major cause of high death rates from cancer in the Republic of Moldova is the low detection rate and detection in advanced stages, an issue that have a negative impact on survival of the person diagnosed with breast cancer (BC). Each year more than 500 women die from their breast cancer (2). Moreover, as costs per treated case can reach up to 2500 euro at stages III-IV, not only chances of survival increases with diagnosis at earlier stages, but considerable costs can be contained if one targets to discover the disease as early as possible. This can be done by systematically using breast cancer screening. By October 2019, women in 28 from 32 national districts were examined and more than 40 cases of BC were found (1).

Description of the intervention:

Breast cancer screening (BCS) in Moldova started in October 2018. As for today, BCS is performed by 4 mobile units with digital mammography: during 1 working week the mobile unit is sent to different national districts according to Ministry of Health, Labor and Social Protection strategy and approved timeline (3). Each mobile unit has a driver and a radiology expert, but do not include a doctor. According to the national plan, each family doctor (general practitioner) inform targeted population (usualy by phone) about the possibility of performing a BCS at a specific date and place, sometimes the targeted population is repeatedly invited (no financial incentives or other funds allocated for the invitation process). After 1 week of working in the district, the mobile unit returns to Chisinau (capital city) and transfer the obtained images (digital mammographies) to Oncology Institute for final examination and final imaging report (2 oncology experts independently review the images).

If an image may indicate BC or a woman is diagnosed with cancer or pre-cancerous disease (BIRADS III, IV, V), the patient is invited to the Oncology Insitute for further examination using breast ultrasound examination (USG) and clinical examination by an

onco-mammology expert. If a localized formation is suspected, a echoed diagnostic puncture is performed. Afterwards, a treatment is prescribed and often surgical treatment is recommended. If breast USG and clinical examination at the onco-mammology expert does not reveal any signs of BC, the patient is required to perform 2 more examinations, one after 3 months and the second after 6 months. If after 2 repeated examinations there are no signs of BC, the patient is cancelled from the list of suspected cases.

How the intervention might work:

Screening tests (e.g. mammography) for breast cancer are in general considered as a safe way to discover women with breast cancer at initial stages where there usually are no clear symptoms (3). Other methods for diagnosing such as MRI and 3D Mammography are also safe, but expensive. USG is cheaper than X-ray mammography, but generates higher number of false positive and false negative results at women younger than 49 years (3).

Why it is important to do this review:

Using international support from NIPH Norway and the collaborating HTA team, the Republic of Moldova HTA core group will write a Health Technology Assessment report using validated methods for systematic review and analyses. As an evidence-based information source, the HTA report will serve decision support to Oncology Institute experts in breast cancer screening to use in revising the current Ministry of Health, Labor and Social Protection policies regarding BCS. HTA report will constitute one major part in the decision support material along with experts considerations related to appropriate age range, economic costs evaluation, feasability and organisational issues addressed, to allow the Government of the Republic of Moldova to submit legal framework changes in national screening protocols currently in use.

METHODS

CLINICAL EFFECT

Literature search:

The Moldova HTA team will determine the PICO question on the topic proposed for HTA by the Ministry of Health, Labor and Social Protection. The research librarian M.G. will use PICO question to elaborate a search strategy that will further be assessed by the HTA core group. The final search strategy protocol will be used by the librarian to obtain maximum relevant hits from 3 different databases (Epistemonikos, PubMed, Cochrane databases will be used). Also, European Union Guidelines on Breast Cancer Screening will be checked for useful information. A second librarian from NIPH will assess the search strategy and the hits obtained. Only articles and guidelines in English language from 2016-2019 period will be used. All the hits obtained will be checked for duplicates (both librarians will perform independently the assessement – M.G. and M.H.).

Selection of relevant studies:

References will be reviewed based on titles and abstracts by 2 HTA core group members (L.B. and S.O.), and the final full-text articles and guidelines list will be proposed for further assessment. After that 2 HTA core group members (A.A. and L.B.) will perform independently the AMSTAR-2 appraisal for each full-text article obtained (4). Based on PICO we will select publications based on relevance and study design. In case we find recent Systematic Reviews (SR) relevant to our question we will use appropriate checklists to assess the quality of them. The HTA team will select the SRs and guidelines which are the most recent ones and with increased certainty of evidence. In the final, we will choose only those articles and guidelines that respond more accurately to the PICO question defined at the beginning.

Data extraction and quality assessment of included systematic reviews:

After the final selection, we will describe the articles, extract data and summarize an evidence table, that will allow the team to extract de estimates for each outcome searched. We will use the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) instrument (5) to assess the certainty of evidence of the evidence, if not already done in the included systematic reviews, we will present estimates of effect and the rating of the certainty of the evidence, as well as the justification for this, in "Summary of Findings" tables according to the GRADE Protocol.

All steps in the selection and extraction processes will be performed independently by two reviewers (S.O. and K.F.). Any disagreement between the reviewers in these processes will be resolved by discussions between members of the project.

Inclusion and exclusion criteria:

Population	Asymptomatic women aged 40-75
Intervention	Imaging technology: mammography (including 3D), MR, Ultrasound
Control	No screening
Outcomes	All cause mortality, Breast cancer-related mortality, HRQoL, Harms (due to false positives), Anxiety, Overdiagnosis
Study designs	RCTs, SR, Guidelines and protocols, HTA
Languages	English
Exclusion criteria	-

HEALTH ECONOMIC EVALUATION:

Based on available data regarding costs per each step of the BCS performed (e.g. cost of the mobile unit, cost of the mamography, financial incentives for workers etc.) (1), we will perform a budget consequence and determine the current and projected treatment cost estimates and budget impact of breast cancer screening in Moldova.

GANTT DIAGRAM

Task	Responsible	Start date	Calender-time in days	Completion date	Actual time used
Write project plan	Project Manager	01.11.2018	30	31.12.2019	60
Technical and professional review of plan	HTA Team	01.01.2019	30	13.03.2019	72
Inception meeting with NIPH	HTA Team	12.02.2019	1	12.02.2019	1
Approval of plan	Project Manager	10.03.2019	5	20.03.2019	10
Literature search	M.G.	26.06.2019	30	01.08.2019	35
Selection of studies	M.G.	01.08.2019	15	14.08.2019	15
Evaluate the methodological quality of the studies	HTA Team	15.08.2019	15	10.09.2019	25
Initial study list shared with NIPH	M.G.	11.09.2019	3	13.09.2019	3
Refined search strategy and updated list of quality-appraised	M.G.	13.09.2019	5	20.09.2019	7
Retrieve data, compile and grade	HTA Team	14.10.2019	60	31.01.2020	107
Preliminary analysis of study results	HTA Team	24.10.2019	30	29.11.2019	35
Preliminary results shareed with NIPH	HTA Team	27.02.2020	16	20.03.2020	22
Write draft report	HTA Team	23.03.2020	60	30.06.2020	95
Technical and professional review of report	HTA Team	01.07.2020	90	04.11.2020	125
Finalise report	HTA Team	01.10.2020	30	31.03.2021	145
Approval and publication	Project Manager	01.11.2020	60	01.05.2021	30

Publication and dissemination:

Final draft report will be assessed independently by 2 HTA experts from NIPH (technical review) and 2 oncology experts from Oncology Institute from the Republic of Moldova (professional review). The final document will be a HTA report on the topic selected by and designed for major national stakeholders in health (MHLSP, NAPH, Oncology Institute). The final report will be distributed accordingly with the current law procedures, mainly with the use of MHLSP official communication and document distribution channels.

Risk analysis:

RISK	**PROBABILITY**	**CONSEQUENCE**
Delay in planned activities	Fair	Delay of the approval and publication of the final report
One or more of the HTA team will not be able to complete the tasks on time (sick leave, parental leave, dismissal)	Fair	Re-training of the new member(s) of the HTA core group

ONLINE INDEXING:

brest neoplasm; mammography; xeromammography; ultrasonography, mammary; magnetic resonance imaging; diffusion magnetic resonace imaging; diffusion tensor imaging; echo-planar imaging; mass screening-methods; ages factors; female; breast neoplasm –prevention&control; diagnosis, differential; review.

REFERENCES:

1. *Sensible data and description of processes were provided by Oncology expert L.S. by using internal access to National Cancer Registry (NCR);*
2. *All data are extracted from NCR and official Ministry of Health, Labor and Social Protection reports.*
3. *Official document of the MHLSP nr.1149 from 15.10.2018;*
4. *https://amstar.ca/index.php;*
5. *https://www.gradeworkinggroup.org/.*

Appendix 2 BI-RADS

Breast Imaging - Reporting and Database System classification:

BI-RADS 0 – the assessment is not complete and breast cancer specialists may recommend additional work-up;

BI-RADS 1 – Negative - With category 1 the breast cancer screening mammogram shows no grouped or suspicious micro calcifications, no well-formed mass, asymmetrical glandular structure and/or no change from any previous exam;

BI-RADS 2 – Benign - is a definitive benign finding and a routine screening. That is, there is something abnormal on mammogram but it is not breast cancer or malignant in any way;

BI-RADS 3 – Probably Benign - radiologist will recommend a follow-up at 6 months. Sometimes on a breast cancer screening mammogram there may be a finding of some kind, but no palpable lesion is present;

BI-RADS 4 – Suspicious or Indeterminate abnormality - is where concern for breast cancer risk begins to increase. The breast cancer physician should recommend a biopsy with BI-RADS category 4. Typically, a lump is present, but does not initially appear to have the morphological characteristics of breast cancer;

BI-RADS 5 – Highly suggestive of malignancy - Doctors assign a category 5 BI-RADS when there is a very high probability of breast cancer. The medical advisor will request an immediate biopsy;

BI-RADS 6 – Known Cancer - indicates a known cancer, proven by biopsy. This category is used when patients undergoing breast cancer treatment have follow-up mammograms.

Appendix 3 Search strategy on articles

Database: PubMed
Date: 26.09.2019
Hits: 284

Search	Query	Items found
#19	Search (#16) OR #17 Filters: Publication date from 2016/01/01 to 2019/12/31	284
#18	Search (#16) OR #17	866
#17	Search (systematic[sb]) AND #14	334
#16	Search (#14) AND #15	861
#15	Search Meta-Analysis[Mesh:NoExp] or systematic* review*[Title/Abstract] or metaanal*[Title/Abstract] or meta anal*[Title/Abstract] or (review[Title/Abstract] and (structured search*[Title/Abstract] or database* search*[Title/Abstract] or systematic* search*[Title/Abstract])) or integrative review*[Title/Abstract] or evidence review*[Title/Abstract]	314500
#14	Search (#3) OR #13	54158
#13	Search ((#6) OR #9) AND #12	23989
#12	Search (#10) OR #11	381958
#11	Search (breast cancer[Title/Abstract] OR breast neoplasm*[Title/Abstract] OR breast tumo*[Title/Abstract] OR mammary cancer*[Title/Abstract] OR malignant neoplasm* of breast[Title/Abstract] OR malignant tumo* of breast[Title/Abstract] OR breast malignant tumo*[Title/Abstract] OR cancer of breast[Title/Abstract] OR human mammary carcinoma[Title/Abstract] OR cancer breast[Title/Abstract] OR breast malignant neoplasm[Title/Abstract] OR breast malignant neoplasms[Title/Abstract] OR cancer mammary[Title/Abstract] OR cancers mammary[Title/Abstract] OR mammary Carcinoma[Title/Abstract] OR mammary Carcinomas[Title/Abstract] OR mammary neoplasm[Title/Abstract] OR mammary neoplasms[Title/Abstract] OR breast carcinoma[Title/Abstract] OR breast carcinomas[Title/Abstract] OR mammary tumo*[Title/Abstract])	313654
#10	Search breast neoplasm[MeSH Terms]	281275
#9	Search (#7) OR #8	575858
#8	Search (Ultrasound [Title/Abstract] OR Echography[Title/Abstract] OR Ultrasonic Imag*[Title/Abstract] OR Medical Sonography[Title/Abstract] OR Ultrasonic Diagnos*[Title/Abstract] OR Computer Echotomography[Title/Abstract] OR Ultrasonic Tomography[Title/Abstract] OR breast imaging*[Title/Abstract] OR ultrasonography[Title/Abstract] OR Sonography[Title/Abstract] OR sonography medical[Title/Abstract])	343687

Search	Query	Items found
#7	Search ("Ultrasonography, mammary"[MeSH Terms]) OR "ultrasonography"[MeSH Terms]	422458
#6	Search (#4) OR #5	751901
#5	Search magnetic resonance Imag*[Title/Abstract] OR magnetic resonance spectroscop*[Title/Abstract] OR magnetic resonance tomograph*[Title/Abstract] OR NMR[Title/Abstract] OR NMRs[Title/Abstract] OR MRI[Title/Abstract] OR MRIs[Title/Abstract] OR fMRI[Title/Abstract] OR fMRIs[Title/Abstract] OR MR tomograph*[Title/Abstract] OR MR imag*[Title/Abstract] OR MR scan[Title/Abstract] OR MR scans[Title/Abstract] OR Zeugmatograph*[Title/Abstract] OR chemical shift Imag*[Title/Abstract] OR proton spin Tomograph*[Title/Abstract] OR spin echo Imag*[Title/Abstract] OR diffusion Tractograph*[Title/Abstract] OR echo planar Imag*[Title/Abstract] OR echoplanar Imag*[Title/Abstract] OR magnetic resonance Angiograph*[Title/Abstract] OR magnetization transfer contrast Imag*[Title/Abstract] OR MR scanning*[Title/Abstract] OR magnetic resonance scan*[Title/Abstract]	599173
#4	Search ("Magnetic Resonance Imaging"[Mesh:NoExp] or "Diffusion Magnetic Resonance Imaging"[Mesh:NoExp] or "Diffusion Tensor Imaging"[Mesh:NoExp] or "Echo-Planar Imaging"[Mesh:NoExp] or "Fluorine-19 Magnetic Resonance Imaging"[Mesh:NoExp] or "Magnetic Resonance Angiography"[Mesh:NoExp] or "Magnetic Resonance Imaging, Cine"[Mesh:NoExp])	428952
#3	Search (#1) OR #2	38287
#2	Search (mammograph*[Title/Abstract] or xeromammograph*[Title/Abstract] or digital breast tomosynthes*[Title/Abstract])	28705
#1	Search (mammography[MeSH Terms]) OR xeromammography[MeSH Terms]	29082

Database: Cochrane Database of Systematic Reviews
Date: 26.09.2019
Hits: 61

Search	**Query**	**Items found**
#1	[mh ^Mammography]]	764
#2	[mh ^xeromammography]	5
#3	(mammograph* or xeromammograph* or "digital breast tomosynthes*"):ti,ab	1967
#4	#1 OR #2 OR #3	2095
#5	[mh ^"Magnetic Resonance Imaging"]	6882

#6	[mh ^"Diffusion Magnetic Resonance Imaging"]	237
#7	[mh ^"Diffusion Tensor Imaging"]	119
#8	[mh ^"Echo-Planar Imaging"]	82
#9	[mh ^"Fluorine-19 Magnetic Resonance Imaging"]	0
#10	[mh ^"Magnetic Resonance Angiography"]	434
#11	[mh ^"Magnetic Resonance Imaging, Cine"]	229
#12	("Magnetic Resonance Imag*" or "magnetic resonance spectroscop*" or "magnetic resonance tomograph*" or "NMR" or "NMRs" or "MRI" or "MRIs" or "fMRI" or "fMRIs" or "MR tomograph*" or "MR imag*" or "MR scan" or "MR scanning*" or "MR scans" or "Zeugmatograph*" or "Chemical Shift Imag*" or "Proton Spin Tomograph*" or "Magnetization Transfer Contrast Imag*" or "Spin Echo Imag*" or "Diffusion Tractograph*" or "Echo Planar Imag*" or "Echoplanar Imag*" or "Magnetic Resonance Angiograph*" or "Magnetic resonance scan*"):ti,ab	22760
#13	#5 OR #6 OR #7 OR #8 OR #9 OR # 10 OR # 11 OR #12	967446
#14	[mh ^"Ultrasonography, Mammary"]	72
#15	[mh ^Ultrasonography]	4690
#16	("ultrasound" or "echography" or "ultrasonic imag*" or "medical sonography" or "ultrasonic diagnos*" or "computer echotomography" or "ultrasonic tomography" or "breast imaging*" or "ultrasonography" or "Sonography" or "sonography medical"):ti,ab	32158
#17	#14 OR #15 OR #16	33753
#18	[mh ^"breast neoplasm"]	11727
#19	(“Breast cancer” or “breast neoplasm*” or “Breast Tumo*” or “Mammary Cancer*” or “Malignant Neoplasm* of Breast” or “Malignant Tumo* of Breast” or “Breast Malignant Tumo*” or “Cancer of Breast” or “Human Mammary Carcinoma” or ”mammary tumo*” or “cancer breast” or “breast malignant neoplasm*” or “cancer* mammary” or "mammary Carcinoma*" or "mammary neoplasm*" or "breast carcinoma*" or "mammary tumo*"):ti,ab	30643
#20	#18 OR #19	31978
#21	#13 OR #17	976899
#22	#20 AND #21	20519
#23	#4 OR #22	21416
#24	#4 OR #22 with Cochrane Library publication date from Jan 2016 to Dec 2019, in Cochrane Reviews and Cochrane Protocols	61

Database: Epistemonikos
Date: 26.09.2019
Hits: 240

Title/Abstract: ("Magnetic resonance imaging" OR "magnetic resonance imagings" OR "MR scanning" OR "MR scannings" OR "magnetic resonance image" OR "magnetic resonance images" OR "magnetic resonance spectroscopy" OR "magnetic resonance tomography" OR NMR OR NMRs OR MRI OR MRIs OR fMRI OR fMRIs OR "MR tomogra-

phy" OR "MR Imaging" OR "MR Imagings" OR "MR Image" OR "MR Images" OR "MR scan" OR "MR scans" OR Zeugmatograph* OR "Chemical Shift Imaging" OR "Chemical Shift Imagings" OR "Chemical Shift Image" OR "Chemical Shift Images" OR "Proton Spin Tomography") AND ("Breast Tumour" OR "Breast Tumours" OR "breast malignant tumour" OR "breast malignant tumours" OR "malignant tumour of breast" OR "malignant tumours of breast" OR "mammary tumour" OR "mammary tumours" OR "Breast cancer" OR "Breast Neoplasm" OR "Breast Neoplasms" OR "Breast Tumor" OR "Breast Tumors" OR "breast malignant tumor" OR "breast malignant tumors" OR "malignant tumor of breast" OR "malignant tumors of breast" OR "malignant neoplasm of breast" OR "malignant neoplasms of breast" OR "Mammary Cancer" OR "Cancer of Breast" OR "Cancer breast" OR "breast malignant neoplasm" OR "breast malignant neoplasms" OR "cancer mammary" OR "cancers mammary" OR "mammary Carcinoma" OR "mammary Carcinomas" OR "mammary neoplasm" OR "mammary neoplasms" OR "breast carcinoma" OR "breast carcinomas" OR "mammary tumor" OR "mammary tumors") - limit to: 2016-2019 = 64 (61 Systematic Reviews, 2 Structured Summary, 1 Broad synthesis)

Title/Abstract: ("Magnetization Transfer Contrast Imaging" OR "Magnetization Transfer Contrast Imagings" OR "Magnetization Transfer Contrast Image" OR "Magnetization Transfer Contrast Images" OR "Spin Echo Imaging" OR "Spin Echo Imagings" OR "Spin Echo Image" OR "Spin Echo Images" OR "Diffusion Tractography" OR "Echo Planar Imaging" OR "Echo Planar Imagings" OR "Echo Planar Image" OR "Echo Planar Images" OR "Echoplanar Imaging" OR "Echoplanar Imagings" OR "Echoplanar Image" OR "Echoplanar Images" OR "Magnetic Resonance Angiography" OR “Ultrasound” OR ”Echography” OR "breast imaging" OR "Medical Sonography" OR "Ultrasonic Diagnosis" OR "ultrasonography" OR "ultrasonic imagings" OR Sonography OR "breast imagings" OR "computer echotomagraphy" OR "ultrasonic imaging" OR "sonography medical" OR "Ultrasonic Tomography") AND ("Breast Tumour" OR "Breast Tumours" OR "breast malignant tumour" OR "breast malignant tumours" OR "malignant tumour of breast" OR "malignant tumours of breast" OR "mammary tumour" OR "mammary tumours" OR "Breast cancer" OR "Breast Neoplasm" OR "Breast Neoplasms" OR "Breast Tumor" OR "Breast Tumors" OR "breast malignant tumor" OR "breast malignant tumors" OR "malignant tumor of breast" OR "malignant tumors of breast" OR "malignant neoplasm of breast" OR "malignant neoplasms of breast" OR "Mammary Cancer" OR "Cancer of Breast" OR "Cancer breast" OR "breast malignant neoplasm" OR "breast malignant neoplasms" OR "cancer mammary" OR "cancers mammary" OR "mammary Carcinoma" OR "mammary Carcinomas" OR "mammary neoplasm" OR "mammary neoplasms" OR "breast carcinoma" OR "breast carcinomas" OR "mammary tumor" OR "mammary tumors") - limit to: 2016-2019 = 46 (43 Systematic Reviews, 2 Structured Summaries, 1 Broad synthesis)

Title/Abstract: (mammograph* or xeromammograph* or "digital breast tomosynthesis" or "digital breast tomosyntheses") - limit to: 2016-2019 = 130 (121 Systematic Reviews, 4 Structured Summaries, 5 Broad synthesis)

Appendix 4 Search strategy on international guidelines

Breast cancer screening – search for international guidelines.

Date: 14.02.2020

Database	Search string(s)	Number of hits	Commentary/ Hit lists
TRIP+ http://www.tripdatabase.com/	**1** mammography **2** ("Magnetic resonance imaging" OR MRI OR ultrasound) AND "breast cancer"	**1** 159 **2** 440	**1** http://www.tripdatabase.com/search?categoryid=16%2C18%2C10%2C9%2C4&criteria=mammography# **2** http://www.tripdatabase.com/search?categoryid=16%2C18%2C10%2C9%2C4&criteria=(%22Magnetic%20resonance%20imaging%22%20OR%20MRI%20OR%20ultrasound)%20AND%20%22breast%20cancer%22
NHS Evidence in Health and Social Care http://www.evidence.nhs.uk/default.aspx	**1** mammography **2** ("Magnetic resonance imaging" OR MRI OR ultrasound) AND "breast cancer"	**1** 93 **2** 224	**1** https://www.evidence.nhs.uk/search?om=[{%22ty%22:[%22Guidance%22]}]&q=mammography&sp=on **2** https://www.evidence.nhs.uk/search?om=[{%22ty%22:[%22Guidance%22]}]&q=(%22Magnetic+resonance+imaging%22+OR+MRI+OR+ultrasound)+AND+%22breast+cancer%22&sp=on
G-I-N https://g-i-n.net/	**1** mammography **2** ("Magnetic resonance imaging" OR MRI OR ultrasound OR screening) AND "breast cancer"	**1** 4 **2** 23	**1** https://g-i-n.net/library/international-guidelines-library/@@guideline_search_results?type=basic&basic-searchable-text=mammography **2** https://g-i-n.net/library/international-guidelines-library/@@guideline_search_results?type=basic&basic-searchable-text=%28%22Magnetic+resonance+imaging%22+OR+MRI+OR+ultrasound+OR+screening%29+AND+%22breast+cancer%22
NICE (UK) http://www.nice.org.uk/	**1** mammography **2** ("Magnetic resonance imaging" OR MRI OR	**1** 6 **2** 14	**1** https://www.nice.org.uk/search?om=[{%22ndt%22:[%22Guidance%22]}]&ps=15&q=mammography&sp=on **2**

	ultrasound OR screening) AND "breast cancer"		https://www.nice.org.uk/search?om=[{%22ndt%22:[%22Guidance%22]}]&ps=15&q=(%22Magnetic+resonance+imaging%22+OR+MRI+OR+ultrasound+OR+screening)+AND+%22breast+cancer%22&sp=on
Guideline central https://www.guidelinecentral.com/summaries/	**1** mammography **2** breast cancer	**1** 1 **2** 36	**1** https://www.guidelinecentral.com/summaries/#term=mammography&type=title **2** https://www.guidelinecentral.com/summaries/#term=breast+cancer&type=title
UpToDate https://www.uptodate.com/contents/search	breast cancer screening	**4** relevant Up-to-date articles and **1** collection of guidelines from around the world	https://www.uptodate.com/contents/search?search=breast%20cancer%20screening&sp=0&searchType=PLAIN_TEXT&source=USER_INPUT&searchControl=TOP_PULLDOWN&searchOffset=1&autoComplete=true&language=en&max=10&index=1~10&autoCompleteTerm=Breast%20cancer%20s
WHO IRIS (Institutional repository for information sharing) http://apps.who.int/iris	**1** All of IRIS: mammography **2** All of IRIS: Magnetic resonance imaging. Filter by Title contains: breast **3** All of IRIS: MRI. Filter by Title contains: breast **4** All of IRIS: ultrasound. Filter by Title contains: breast	**1** 503 **2** 3 **3** 5 **4** 11	**1** https://apps.who.int/iris/discover?query=mammography **2** https://apps.who.int/iris/discover?filtertype_1=title&filter_relational_operator_1=contains&filter_1=breast&submit_apply_filter=&query=magnetic+resonance+imaging&scope=%2F **3** https://apps.who.int/iris/discover?filtertype_1=title&filter_relational_operator_1=contains&filter_1=breast&submit_apply_filter=&query=MRI **4** https://apps.who.int/iris/discover?filtertype_1=title&filter_relational_operator_1=contains&filter_1=breast&submit_apply_filter=&query=ultrasound&scope=%2F
European	**1** mammogra-	**1** 50	The Commission has their own guidelines

Commission Initiative on Breast Cancer https://healthcare-quality.jrc.ec.europa.eu/	phy **2** MRI **3** Magnetic resonance imaging **4** ultrasound **5** screening	**2** 7 **3** 7 **4** 9 **5** 118	(https://healthcare-quality.jrc.ec.europa.eu/european-breast-cancer-guidelines), as well as a collection on international guidelines on breast cancer care. **1** https://healthcare-quality.jrc.ec.europa.eu/search/node?keys=mammography **2** https://healthcare-quality.jrc.ec.europa.eu/search/node?keys=MRI **3** https://healthcare-quality.jrc.ec.europa.eu/search/node?keys=Magnetic+resonance+imaging **4** https://healthcare-quality.jrc.ec.europa.eu/search/node?keys=ultrasound **5** https://healthcare-quality.jrc.ec.europa.eu/search/node?keys=screening

Manual search in Internet (sources with no search engine, or small content)		
Database	**Number of relevant hits**	**Commentary**
SIGN http://www.sign.ac.uk/ (Scotland)	0	Looked at the guidelines in the category "Cancer"
European Society For Medical Oncology https://www.esmo.org/guidelines/	0	Looked at the guidelines in the category "Breast Cancer"
Ministry of Health - New Zealand https://www.health.govt.nz/publications?f%5B0%5D=im_field_publication	0	Looked at the publications in the category "Cancer"

_type%3A26		
CMA INFOBASE (Canada) http://www.cma.ca/clinicalresources/practiceguidelines	5	Looked at the guidelines in the category "Breast Cancer" The relevant guidelines are listed below. (Complete list is found here: https://joulecma.ca/cpg/homepage/browse-by/category/conditions/id/68)
CTFPHC (Canadian Task Force on Preventive Health Care) http://canadiantaskforce.ca/	2	Looked over the guidelines listed.
https://www.cancer.org/healthy/find-cancer-early/cancer-screening-guidelines.html	3	Looked over the guidelines listed.
https://www.cancer.org/health-care-professionals/american-cancer-society-prevention-early-detection-guidelines/breast-cancer-screening-guidelines.html	4	Looked over the guidelines listed.
http://www.who.int/publications/guidelines/en/	1	Looked over the guidelines listed. https://www.who.int/publications/guidelines/year/en/ https://www.who.int/cancer/publications/mammography _screening/en/

Relevant hits from CMA INFOBASE

1. Effectiveness of screening with annual magnetic resonance imaging and mammography: results of the initial screen from the Ontario High Risk Breast Screening Program
Cancer Care Ontario's Program in Evidence-based Care
Published on: 2014-06
Details

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2. Breast screening for survivors of breast cancer
Cancer Care Ontario's Program in Evidence-based Care
Published on: 2017-09
Details

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3. Magnetic resonance imaging screening of women at high risk for breast cancer
Cancer Care Ontario's Program in Evidence-based Care
Published on: 2018-01
Details

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4. Recommendations on screening for breast cancer in women aged 40–74 years who are not at increased risk for breast cancer
Canadian Task Force on Preventive Health Care
Published on: 2018-12
Details

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5. Choosing Wisely Canada recommendation - Don't routinely do screening mammography for average risk women aged 40 – 49. Individual assessment of each woman's preferences and risk should guide the discussion and decision regarding mammography screening in this age group
College of Family Physicians of Canada
Published on: 2019-07
Details

Relevant hits from WHO IRIS:

Guidelines for the early detection and screening of breast cancer: quick reference guide

World Health Organization, Regional Office for the Eastern Mediterranean (2006)
(Match found in full text)

Guidelines for the early detection and screening of breast cancer

World Health Organization, Regional Office for the Eastern Mediterranean (2006)
(Match found in full text)

Guidelines for management of breast cancer

World Health Organization, Regional Office for the Eastern Mediterranean (2006)
(Match found in full text)

WHO position paper on mammography screening

World Health Organization (2014)
Subject: Mammography...

Screening programmes: a short guide. Increase effectiveness, maximize benefits and minimize harm

World Health Organization. Regional Office for Europe (2020)
(Match found in full text)

WHO report on cancer: setting priorities, investing wisely and providing care for all

World Health Organization (2020)

Screening: when is it appropriate and how can we get it right?

World Health Organization. Regional Office for Europe; European Observatory on Health Systems and Policies; Sagan A; McDaid D; Rajan S; Farrington J; McKee M (2020)
(Match found in full text)

Guide to cancer early diagnosis

World Health Organization (2017)

(Match found in full text)

Early detection of cancers common in the Eastern Mediterranean Region

World Health Organization, Regional Office for the Eastern Mediterranean (2017)

(Match found in full text)

WHO list of priority medical devices for cancer management

World Health Organization (2017)

(Match found in full text)

World Health Organization. (2008). Diagnosis and treatment. World Health Organization. Https://apps.who.int/iris/handle/10665/43827

National cancer control programmes: policies and managerial guidelines, 2nd ed.

National cancer control programmes : policies and managerial guidelines : executive summary

World Health Organization (2002)

Relevant hits from CTFPHC (Canadian Task Force on Preventive Health Care)

https://canadiantaskforce.ca/guidelines/published-guidelines/breast-cancer/

https://canadiantaskforce.ca/guidelines/published-guidelines/breast-cancer-update/

Relevant hits from https://www.cancer.org/healthy/find-cancer-early/cancer-screening-guidelines.html

American Cancer Society Breast Cancer Screening Guideline (2015)

American Cancer Society Guideline for Breast Screening with MRI as an Adjunct to Mammography (2007)

For Your Patients: Breast Cancer Early Detection

Supplementary Materials: Breast Cancer Risk Assessment

Relevant hits from https://www.who.int/publications/guidelines/year/en/

WHO position paper on mammography screening

https://www.who.int/cancer/publications/mammography_screening/en/

Appendix 5 Inclusion and exclusion process

Inclusion and exclusion on international guidelines

N	Reference	Inclusion /exclusion	Reason for exclusion
1	**WHO position paper on mammography screening** ISBN: 978 92 4 150793 6 **Web source**: https://www.who.int/cancer/publications/mammography_screening/en/	Exclude	Did not use GRADE-tool as quality assessment tool and were updated in a more recent publication;
2	**European breast cancer guidelines: Screening ages and frequencies** Women aged 40-44; aged 45-49; aged 50-69; aged 70-74. **Web source:** a) Overall guidelines ref: https://healthcare-quality.jrc.ec.europa.eu/european-breast-cancer-guidelines/screening-ages-and-frequencies b) Evidence (SR) for 40-44: https://healthcare-quality.jrc.ec.europa.eu/european-breast-cancer-guidelines/screening-ages-and-frequencies/women-40-44 c) Evidence (SR) for 45-49: https://healthcare-quality.jrc.ec.europa.eu/european-breast-cancer-guidelines/screening-ages-and-frequencies/women-45-49 d) Evidence (SR) for 50-69: https://healthcare-quality.jrc.ec.europa.eu/european-breast-cancer-guidelines/screening-ages-and-frequencies/women-50-69 e) Evidence (SR) for 70-74: https://healthcare-quality.jrc.ec.europa.eu/european-breast-cancer-guidelines/screening-ages-and-frequencies/women-70-74	**Include**	Answers PICO; Used GRADE-tool as quality assessment tool; Were updated recently (October 2019).
3	**Breast Cancer Update (2018)** Recommendations on screening for breast cancer in women 40-74 years of age who are not at increased risk the Canadian Task Force on Preventive Health Care Klarenbach S, Sims-Jones N, Lewin G, Singh H, Thériault G, Tonelli M , et al **Web source:** https://canadiantaskforce.ca/guidelines/published-guidelines/breast-cancer-update/	Exclude	Did not use GRADE-tool as quality assessment tool and were updated in a more recent publication;
4	**Choosing Wisely Canada recommendation** Don't routinely do screening mammography for average risk women aged 40 – 49. Individual assessment of each woman's preferences and risk should guide the discussion and decision regarding mammography screening in this age group 2019-July **Web source:** https://joulecma.ca/cpg/search/view/19484	Exclude	Did not use GRADE-tool as quality assessment tool and were updated in a more recent publication;
5	**Overdiagnosis from mammographic screening** **Web source:** https://canceraustralia.gov.au/publications-and-resources/position-statements/overdiagnosis-mammographic-screening	Exclude	Not an SR, RCT or HTA

Inclusion and exclusion on selected articles

Nr	Article	Decision	Arguments
1	Martínez-Alonso M, Carles-Lavila M, Pérez-Lacasta MJ, Pons-Rodríguez A, Garcia M, Rué M, et al. Assessment of the effects of decision aids about breast cancer screening: a systematic review and meta-analysis. BMJ open 2017;7(10):e016894.	Exclude	Aim: effect of decision aid, not our aim. Not our intervention
2	Chen THH, Yen AMF, Fann JCY, Gordon P, Chen SLS, Chiu SYH, et al. Clarifying the debate on population-based screening for breast cancer with mammography: A systematic review of randomized controlled trials on mammography with Bayesian meta-analysis and causal model. Medicine (United States) 2017;96(3):e5684.	Exclude	Does not correspond to PICO
3	Zhang XH, Xiao C. Diagnostic Value of Nineteen Different Imaging Methods for Patients with Breast Cancer: a Network Meta-Analysis. Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology 2018;46(5):2041-55.	Exclude	Not our interventions, not our PICO, not our age range. Comparing of different screening methods
4	Jacklyn G, Glasziou P, Macaskill P, Barratt A. Meta-analysis of breast cancer mortality benefit and overdiagnosis adjusted for adherence: Improving information on the effects of attending screening mammography. Br J Cancer 2016;114(11):1269-76.	Exclude	Focus on overdiagnosis.
5	Vang S, Margolies LR, Jandorf L. Mobile Mammography Participation Among Medically Underserved Women: A Systematic Review. Prev Chronic Dis 2018;15:E140.	Exclude	Not our scope: Stationary vs mobile mammography
6	Demb J, Akinyemiju T, Allen I, Onega T, Hiatt RA, Braithwaite D. Screening mammography use in older women according to health status: a systematic review and meta-analysis. Clin Interv Aging 2018;13:1987-97.	Exclude	Screening according to health status
7	Ivlev I, Hickman EN, McDonagh MS, Eden KB. Use of patient decision aids increased younger women's reluctance to begin screening mammography: a systematic review and meta-analysis. J Gen Intern Med 2017;32(7):1-10.	Exclude	Aim: Decision aids Intervention is the use of decision aid
8	Mandrik O, Ekwunife OI, Zielonke N, Meheus F, Severens JL, Lhachimi SK, et al. What determines the effects and costs of breast cancer screening? A protocol of a systematic review of reviews. Systematic reviews 2017;6(1):122.	Exclude	Protocol, not a systematic review
9	Krager SC, Prochazka AV. 2016 - Review: In women 50 to 69 y of age at average risk, mammography screening reduces breast cancer mortality. ACP J Club 2016;164(8):1-.	Exclude	Relates to Nelson HD 2016 Update on 2009 US recommendations.

10	Krager SC, Prochazka AV. 2016 - Review: In women ≥ 40 years of age at average risk, breast cancer screening causes some harms. ACP J Club 2016;164(8):2-.	Exclude	Relates to Nelson HD 2016 Update on 2009 US recommendations.
11	van den Ende C, Oordt-Speets AM, Vroling H, van Agt HME. Benefits and harms of breast cancer screening with mammography in women aged 40-49 years: A systematic review. Int J Cancer 2017;141(7):1295-306.	**Include**	**Answers PICO related questions**
12	Broeders MJM, Allgood P, Duffy SW, Hofvind S, Nagtegaal ID, Paci E, et al. The impact of mammography screening programmes on incidence of advanced breast cancer in Europe: a literature review. BMC Cancer 2018;18(1):860.	Exclude	Not an RCT Not relevant to PICO
13	Schiller-Frühwirth IC, Jahn B, Arvandi M, Siebert U. Cost-Effectiveness Models in Breast Cancer Screening in the General Population: A Systematic Review. Applied health economics and health policy 2017;15(3):1-19.	Exclude	CEA will be researched separately
14	Nelson HD, Fu R, Cantor A, Pappas M, Daeges M, Humphrey L. Effectiveness of Breast Cancer Screening: Systematic Review and Meta-analysis to Update the 2009 U.S. Preventive Services Task Force Recommendation Ann Intern Med 2016;164(4):244-55.	**Include**	**Answers PICO related questions**
15	Copeland VC, Kim YJ, Eack SM. Effectiveness of Interventions for Breast Cancer Screening in African American Women: A Meta-Analysis. Health Serv Res 2018;53 Suppl 1:3170-88.	Exclude	Relates to Afro-American women (different socio-economic determinants)
16	Wozniacki P, Skokowski J, Bartoszek K, Kosowska A, Kalinowski L, Jaskiewicz J. The impact of the Polish mass breast cancer screening program on prognosis in the Pomeranian Province. Arch Med Sci 2017;13(2):441-7.	Exclude	Only a pilot study in a small district in Poland No nationwide BCS program established
17	Mandrik O, Zielonke N, Meheus F, Severens JLH, Guha N, Herrero Acosta R, et al. Systematic reviews as a "lens of evidence": determinants of benefits and harms of breast cancer screening. Int J Cancer 2019;145(4):994-1006.	**Include**	**Answers PICO related questions**
18	Xuan-Anh Phi, Alberto Ragliafico, Nehmat Houssami, Marcel J.W. Greuter, Geertruida H. De Bock Digital breast tomosynthesis for breast cancer screening and diagnosis in women with dense breasts – a systematic review and meta-analysis. BMC Cancer (2018) 18:380	Exclude	Not an economic option for Republic of Moldova BCS program at this stage

Appendix 6 Data extraction on 3 SRs selected

Article 1: Van den Ende C, Oordt-Speets AM, Vroling H, van Agt HME. Benefits and harms of breast cancer screening with mammography in women aged 40-49 years: A systematic review. Int J Cancer 2017; 141(7):1295-306.	
Date of literature search:	The electronic databases Embase, Medline (OvidSP), Cochrane Library and PubMed from inception to 21 February 2017.
Quality of the systematic review according to checklist:	High
Study designs included:	Only Randomized controlled trials (RCTs) published in English language were searched. Limits were: no conference abstracts, conference papers, letters or editorials.
Patients	Women aged 40-49 years from general population
Intervention and comparisons	(any type of) mammography screening (versus no screening); Follow-up time of at least 10 years after randomization; Sample size of at least 40000;
Outcomes measured	Relative reduction in breast cancer-related mortality or all-cause mortality; Proportions of negative effects due to breast cancer screening with mammography (proportion of false-positive/false-negative results, chance of over-diagnosis of breast cancer, risk of radiation)
Article 2: Mandrik O, Zielonke N, Meheus F, Severens JLH, Guha N, Herrero Acosta R, et al. Systematic reviews as a "lens of evidence": determinants of benefits and harms of breast cancer screening. Int. J. Cancer 2019; 145(4):994-1006.	
Date of literature search:	The authors searched the PubMed via Medline, Scopus, Embase and Cochrane databases in August 2016 and conducted updates and searches for grey literature in February 2917 and again in April 2018
Quality of the systematic review according to checklist:	High
Study designs included:	Systematic reviews, RCTs, (including Meta-analysis), observational studies
Patients	Women among all age groups (with focus on women aged 50 to 69 years)
Intervention and comparisons	Benefits and harms of Screening mammography in different age groups, different countries and continents Mammography vs. Ultrasonography vs. Clinical Breast Examination vs. Breast Self Examination
Outcomes measured	Mortality, Overdiagnosis, False positive results, Breast cancer screening-induced deaths
Article 3: Nelson HD, Pappas M, Cantor A, Griffin J, Daeges M, Humphrey L. Ann Harms of Breast Cancer Screening: Systematic Review to Update the 2009 U.S. Preventive Services Task Force Recommendation Intern Med 2016; 164(4):256-67.	
Date of literature search:	MEDLINE and Cochrane databases through December 2014
Quality of the systematic review according to checklist:	High
Study designs included:	English-language systematic reviews, randomized trials, and observational studies of screening
Patients	Women aged 40 to 49 years, and 50 to 74 years
Intervention and comparisons	Differences between screening modalities (mammography vs. tomosynthesis vs. clinical breast examination) vs. mammography alone
Outcomes measured	False positive, Overdiagnosis, Anxiety, distress and other psychological responses, Pain during procedures, Radiation exposure

Appendix 7 AMSTAR-2 on 3 selected articles (prior to including the European guidelines)

AMSTAR-2: a critical appraisal tool for systematic reviews that include randomized or non-randomized studies of healthcare interventions, or both

Article 1: van den Ende C, Oordt-Speets AM, Vroling H, van Agt HME. Benefits and harms of breast cancer screening with mammography in women aged 40-49 years: A systematic review. Int J Cancer 2017;141(7):1295-306.

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:
- ⌡ **Population**
- ⌡ **Intervention**
- ⌡ **Comparator group**
- ⌡ **Outcome**

Optional (recommended)
- ⌡ Timeframe for follow-up

☐ **Yes**
☐ No

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:
The authors state that they had a written protocol or guide that included ALL the following:
- ⌡ **review question(s)**
- ⌡ **a search strategy**
- ⌡ **inclusion/exclusion criteria**
- ⌡ **a risk of bias assessment**

For Yes:
As for partial yes, plus the protocol should be registered and should also have specified:
- ⌡ a meta-analysis/synthesis plan, if appropriate, *and*
- ⌡ a plan for investigating causes of heterogeneity
- ⌡ justification for any deviations from the protocol

☐ **Yes**
☐ Partial Yes
☐ No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:
- ⌡ ***Explanation for* including only RCTs**
- ⌡ OR *Explanation for* including only NRSI
- ⌡ OR *Explanation for* including both RCTs and NRSI

☐ **Yes**
☐ No

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):
- ⌡ **searched at least 2 databases (relevant to research question)**
- ⌡ **provided key word and/or search strategy**
- ⌡ **justified publication restrictions (e.g. language)**

For Yes, should also have (all the following):
- ⌡ searched the reference lists / bibliographies of included studies
- ⌡ searched trial/study registries
- ⌡ included/consulted content experts in the field
- ⌡ where relevant, searched for grey literature
- ⌡ conducted search within 24 months of completion of the review

☐ **Yes**
☐ Partial Yes
☐ No

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:

- **at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include**
- OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

- **Yes**
- No

6. Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:

- at least two reviewers achieved consensus on which data to extract from included studies
- OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.

- Yes
- **No**

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes:

- provided a list of all potentially relevant studies that were read in full-text form but excluded from the review

For Yes, must also have:

- **Justified the exclusion from the review of each potentially relevant study**

- **Yes**
- Partial Yes
- No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):

- **described populations**
- **described interventions**
- **described comparators**
- **described outcomes**
- **described research designs**

For Yes, should also have ALL the following:

- described population in detail
- described intervention in detail (including doses where relevant)
- described comparator in detail (including doses where relevant)
- described study's setting
- timeframe for follow-up

- **Yes**
- Partial Yes
- No

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs

For Partial Yes, must have assessed RoB from

- unconcealed allocation, *and*
- lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)

For Yes, must also have assessed RoB from:

- **allocation sequence that was not truly random, *and***
- **selection of the reported result from among multiple measurements or analyses of a specified outcome**

- **Yes**
- Partial Yes
- No
- Includes only NRSI

NRSI

For Partial Yes, must have assessed RoB:

- from confounding, *and*
- from selection bias

For Yes, must also have assessed RoB:

- methods used to ascertain exposures and outcomes, *and*
- selection of the reported result from among multiple measurements or analyses of a specified outcome

- Yes
- Partial Yes
- No
- **Includes only RCTs**

10. Did the review authors report o n the sources of funding for the studies included in the review?

For Yes

- Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies

☐ Yes
☐ **No**

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs

For Yes:

- The authors justified combining the data in a meta-analysis
  - AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.
  - AND investigated the causes of any heterogeneity

- Yes
- No
- **No meta-analysis conducted**

For NRSI

For Yes:

- The authors justified combining the data in a meta-analysis
  - AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present
  - AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available
  - AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review

- Yes
- No
- No meta-analysis conducted

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

For Yes:

- included only low risk of bias RCTs
- OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.

- Yes
- No
- **No meta-analysis conducted**

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?

For Yes:

- included only low risk of bias RCTs
- **OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results**

- **Yes**
- No

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

For Yes:

- There was no significant heterogeneity in the results
- **OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review**

- **Yes**
- No

15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

For Yes:

- performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias

- Yes
- No
- **No meta-analysis conducted**

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

For Yes:

- ☐ The authors reported no competing interests OR
- ☐ The authors described their funding sources and how they managed potential conflicts of interest

- ☐ Yes
- ☐ **No**

Article 2: Nelson HD, Fu R, Cantor A, Pappas M, Daeges M, Humprey L. Effectiveness of Breast Cancer Screening: Systematic Review and Meta-analysis to Update the 2009 U.S. Preventive Services Task Force Recommendation; Ann Intern Med 2016;164(4):244-55.

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:

- ☐ **Population**
- ☐ **Intervention**
- ☐ **Comparator group**
- ☐ **Outcome**

Optional (recommended)

- ☐ Timeframe for follow-up

- ☐ **Yes**
- ☐ No

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:
The authors state that they had a written protocol or guide that included ALL the following:

- ☐ **review question(s)**
- ☐ **a search strategy**
- ☐ **inclusion/exclusion criteria**
- ☐ **a risk of bias assessment**

For Yes:
As for partial yes, plus the protocol should be registered and should also have specified:

- ☐ a meta-analysis/synthesis plan, if appropriate, *and*
- ☐ a plan for investigating causes of heterogeneity
- ☐ justification for any deviations from the protocol

- ☐ **Yes**
- ☐ Partial Yes
- ☐ No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:

- ☐ *Explanation for* including only RCTs
- ☐ OR *Explanation for* including only NRSI
- ☐ **OR *Explanation for* including both RCTs and NRSI**

- ☐ **Yes**
- ☐ No

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):

- ☐ **searched at least 2 databases (relevant to research question)**
- ☐ **provided key word and/or search strategy**
- ☐ **justified publication restrictions (e.g. language)**

For Yes, should also have (all the following):

- ☐ searched the reference lists / bibliographies of included studies
- ☐ searched trial/study registries
- ☐ included/consulted content experts in the field
- ☐ where relevant, searched for grey literature
- ☐ conducted search within 24 months of completion of the review

- ☐ Yes
- ☐ **Partial Yes**
- ☐ No

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:

- at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

- Yes
- **No**

6. Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:

- at least two reviewers achieved consensus on which data to extract from included studies
- OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.

- Yes
- **No**

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes:

- provided a list of all potentially relevant studies that were read in full-text form but excluded from the review

For Yes, must also have:

- **Justified the exclusion from the review of each potentially relevant study**

- **Yes**
- Partial Yes
- No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):

- described populations
- described interventions
- described comparators
- described outcomes
- described research designs

For Yes, should also have ALL the following:

- **described population in detail**
- **described intervention in detail (including doses where relevant)**
- **described comparator in detail (including doses where relevant)**
- **described study's setting**
- **timeframe for follow-up**

- **Yes**
- Partial Yes
- No

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs

For Partial Yes, must have assessed RoB from

- **unconcealed allocation,** *and*
- lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)

For Yes, must also have assessed RoB from:

- allocation sequence that was not truly random, *and*
- selection of the reported result from among multiple measurements or analyses of a specified outcome

- Yes
- **Partial Yes**
- No
- Includes only NRSI

NRSI

For Partial Yes, must have assessed RoB:

- from confounding, *and*
- from selection bias

For Yes, must also have assessed RoB:

- methods used to ascertain exposures and outcomes, *and*
- selection of the reported result from among multiple measurements or analyses of a specified outcome

- Yes
- Partial Yes
- No
- Includes only RCTs

10. Did the review authors report on the sources of funding for the studies included in the review?

For Yes

- ⎕ **Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies**

  ☐ **Yes**
  ☐ No

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs

For Yes:

- ⎕ **The authors justified combining the data in a meta-analysis**
  - ⎕ **AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.**
  - ⎕ **AND investigated the causes of any heterogeneity**

⎕ **Yes**
⎕ No
⎕ No meta-analysis conducted

For NRSI

For Yes:

- ⎕ The authors justified combining the data in a meta-analysis
  - ⎕ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present
  - ⎕ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available
  - ⎕ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review

⎕ Yes
⎕ No
⎕ **No meta-analysis conducted**

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

For Yes:

- ⎕ **included only low risk of bias RCTs**
- ⎕ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.

⎕ **Yes**
⎕ No
⎕ No meta-analysis conducted

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?

For Yes:

- ⎕ **included only low risk of bias RCTs**
- ⎕ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results

⎕ **Yes**
⎕ No

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

For Yes:

- ⎕ There was no significant heterogeneity in the results
- ⎕ **OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review**

⎕ **Yes**
⎕ No

15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

For Yes:

- ⎕ **performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias**

⎕ **Yes**
⎕ No
⎕ No meta-analysis conducted

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

For Yes:
- The authors reported no competing interests OR
- **The authors described their funding sources and how they managed potential conflicts of interest**

- **Yes**
- No

Article 3: Mandrik O, Zielonke N, Meheus F, Severens JLH, Guha N, Herrero Acosta R, et al. Systematic reviews as a "lens of evidence": determinants of benefits and harms of breast cancer screening.
Int J Cancer 2019;145(4):994-1006.

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:
- Population
- **Intervention**
- **Comparator group**
- **Outcome**

Optional (recommended)
- Timeframe for follow-up

- **Yes**
- No

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:
The authors state that they had a written protocol or guide that included ALL the following:
- review question(s)
- a search strategy
- inclusion/exclusion criteria
- **a risk of bias assessment**

For Yes:
As for partial yes, plus the protocol should be registered and should also have specified:
- a meta-analysis/synthesis plan, if appropriate, *and*
- a plan for investigating causes of heterogeneity
- **justification for any deviations from the protocol**

- Yes **Partial Yes**
- No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:
- *Explanation for* including only RCTs
- OR *Explanation for* including only NRSI
- OR *Explanation for* including both RCTs and NRSI

- Yes
- **No**

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):
- **searched at least 2 databases (relevant to research question)**
- **provided key word and/or search strategy**
- **justified publication restrictions (e.g. language)**

For Yes, should also have (all the following):
- searched the reference lists / bibliographies of included studies
- searched trial/study registries
- included/consulted content experts in the field
- where relevant, searched for grey literature
- conducted search within 24 months of completion of the review

- Yes **Partial Yes**
- No

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:

- at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

- Yes
- **No**

6. Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:

- at least two reviewers achieved consensus on which data to extract from included studies
- OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.

- Yes
- **No**

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes:

- provided a list of all potentially relevant studies that were read in full-text form but excluded from the review

For Yes, must also have:

- **Justified the exclusion from the review of each potentially relevant study**

- **Yes**
- Partial Yes
- No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):

- described populations
- described interventions
- described comparators
- described outcomes
- described research designs

For Yes, should also have ALL the following:

- **described population in detail**
- **described intervention in detail (including doses where relevant)**
- **described comparator in detail (including doses where relevant)**
- **described study's setting**
- **timeframe for follow-up**

- **Yes**
- Partial Yes
- No

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs

For Partial Yes, must have assessed RoB from

- unconcealed allocation, *and*
- lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)

For Yes, must also have assessed RoB from:

- allocation sequence that was not truly random, *and*
- selection of the reported result from among multiple measurements or analyses of a specified outcome

- Yes
- Partial Yes
- **No**
- Includes only NRSI

NRSI

For Partial Yes, must have assessed RoB:

- from confounding, *and*
- from selection bias

For Yes, must also have assessed RoB:

- methods used to ascertain exposures and outcomes, *and*
- selection of the reported result from among multiple measurements or analyses of a specified outcome

- Yes
- Partial Yes
- No
- Includes only RCTs

10. Did the review authors report o n the sources of funding for the studies included in the review?

For Yes

- **Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies** — **Yes** / No

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs

For Yes:

- **The authors justified combining the data in a meta-analysis**
  - **AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.**
    - AND investigated the causes of any heterogeneity

Yes / No / No meta-analysis conducted

For NRSI

For Yes:

- The authors justified combining the data in a meta-analysis
  - AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present
    - AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available
      - AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review

Yes / No / No meta-analysis conducted

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

For Yes:

- included only low risk of bias RCTs
- OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.

Yes / **No** / No meta-analysis conducted

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?

For Yes:

- included only low risk of bias RCTs
- OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results

Yes / **No**

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

For Yes:

- There was no significant heterogeneity in the results
- **OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review**

Yes / No

15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

For Yes:

- performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias

Yes / **No** / No meta-analysis conducted

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	
For Yes: ☐ The authors reported no competing interests OR ☐ **The authors described their funding sources and how they managed potential conflicts of interest**	☐ **Yes** ☐ No

Appendix 8 AMSTAR-2 on SRs supporting the EU-guidelines

JRC Technical report (2020) unpublished entitled "Questions 1-3: Should mammography screening vs. no mammography screening be used for detecting breast cancer in women?

1. Did the research questions and inclusion criteria for the review include the components of PICO?		
For Yes: ☐ Population ☐ **Intervention** ☐ **Comparator group** ☐ **Outcome**	Optional (recommended) ☐ Timeframe for follow-up	☐ **Yes** ☐ No
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?		
For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following: ☐ review question(s) ☐ a search strategy ☐ inclusion/exclusion criteria ☐ **a risk of bias assessment**	For Yes: **As for partial yes, plus the protocol should be registered and should also have specified:** ☐ a meta-analysis/synthesis plan, if appropriate, *and* ☐ a plan for investigating causes of heterogeneity ☐ **justification for any deviations from the protocol**	☐ **Yes** ☐ Partial Yes ☐ No
3. Did the review authors explain their selection of the study designs for inclusion in the review?		
For Yes, the review should satisfy ONE of the following: ☐ *Explanation for* including only RCTs ☐ OR *Explanation for* including only NRSI ☐ OR *Explanation for* including both RCTs and NRSI		☐ **Yes** ☐ No
4. Did the review authors use a comprehensive literature search strategy?		
For Partial Yes (all the following): ☐ **searched at least 2 databases (relevant to research question)** ☐ **provided key word and/or search strategy** ☐ **justified publication restrictions**	For Yes, should also have (all the following): ☐ searched the reference lists / bibliographies of included studies ☐ searched trial/study registries	☐ Yes ☐ **Partial Yes** ☐ No

(e.g. language)	⎦ included/consulted content experts in the field ⎦ where relevant, searched for grey literature ⎦ conducted search within 24 months of completion of the review	

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:

⎦ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include

⎦ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

□ **Yes**
□ No

6. Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:

⎦ at least two reviewers achieved consensus on which data to extract from included studies

⎦ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.

⎦ **Yes**
⎦ No

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes:	For Yes, must also have:	
⎦ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review	⎦ **Justified the exclusion from the review of each potentially relevant study**	⎦ **Yes** ⎦ Partial Yes ⎦ No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):	For Yes, should also have ALL the following:	
⎦ described populations ⎦ described interventions ⎦ described comparators ⎦ described outcomes ⎦ described research designs	⎦ **described population in detail** ⎦ **described intervention in detail (including doses where relevant)** ⎦ **described comparator in detail (including doses where relevant)** ⎦ **described study's setting** ⎦ **timeframe for follow-up**	⎦ **Yes** ⎦ Partial Yes ⎦ No

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs

For Partial Yes, must have assessed RoB from	For Yes, must also have assessed RoB from:	
⎦ unconcealed allocation, *and* ⎦ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)	⎦ allocation sequence that was not truly random, *and* ⎦ selection of the reported result from among multiple measurements or analyses of a specified outcome	⎦ **Yes** ⎦ Partial Yes ⎦ No ⎦ Includes only NRSI

NRSI

For Partial Yes, must have assessed RoB:

- ⎦ from confounding, *and*
- ⎦ from selection bias

For Yes, must also have assessed RoB:

- ⎦ methods used to ascertain exposures and outcomes, *and*
- ⎦ selection of the reported result from among multiple measurements or analyses of a specified outcome

- ⎦ Yes
- ⎦ Partial Yes
- ⎦ No
- ⎦ **Includes only RCTs and SRs of observational studies**

10. Did the review authors report on the sources of funding for the studies included in the review?

For Yes

- ⎦ **Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information it was not reported by study authors also qualifies**

- Yes
- **Unclear**

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs

For Yes:

- ⎦ **The authors justified combining the data in a meta-analysis**
  - ⎦ **AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.**
  - ⎦ AND investigated the causes of any heterogeneity

- ⎦ **Yes**
- ⎦ No
- ⎦ No meta-analysis conducted

For NRSI

For Yes:

- ⎦ The authors justified combining the data in a meta-analysis
  - ⎦ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present
  - ⎦ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available
  - ⎦ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review

- ⎦ Yes
- ⎦ No
- ⎦ **No meta-analysis conducted**

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

For Yes:

- ⎦ included only low risk of bias RCTs
- ⎦ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.

- ⎦ **Yes**
- ⎦ No
- ⎦ No meta-analysis conducted

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?

For Yes:

- ⎦ included only low risk of bias RCTs
- ⎦ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results

- ⎦ **Yes**
- ⎦ No

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

For Yes:

- There was no significant heterogeneity in the results
- **OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review**

- **Yes**
- No

15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

For Yes:

- performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias

- Yes
- **No**
- No meta-analysis conducted

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

For Yes:

- The authors reported no competing interests OR
- **The authors described their funding sources and how they managed potential conflicts of interest**

- Yes
- **No**