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## Training health workers in clinical breast examination for early detection of breast cancer in low- and middle-income countries (Protocol)

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[Intervention Protocol]

# Training health workers in clinical breast examination for early detection of breast cancer in low- and middle-income countries

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## ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess whether training in CBE improves the ability of health workers in LMICs to detect early breast cancer.

## BACKGROUND

### Description of the condition

The worldwide incidence of breast cancer increased by 3.1% annually between 1980 and 2010 (Forouzanfar 2011) and an estimated 1.677 million new cases were reported in 2012 (Ferlay 2015). This represents 25% of all reported cancer cases (Ferlay 2015). According to the International Agency for Research on Cancer (IARC) GLOBOCAN 2012 database, incidence rates of breast cancer are lower in low- and middle-income countries (LMICs) than in high-income countries, but both overall incidence (number of cases) and age-specific incidence appear to be rising in LMICs. A modelling study obtained registry data on the incidence of breast and

cervical cancer spanning a period of 30 years (1980 to 2010) and covering 187 countries, and reported that twice as many cases of breast cancer occurred in individuals aged 15 to 49 years in developing countries than occurred in the same population in the developed world (Forouzanfar 2011). This may be attributed to population growth, increasing life expectancy and a relative decrease in the burden of infectious diseases, or it may be the result of changes in lifestyle-related risk factors due to urbanisation and economic development (Torre 2015). As an example, women in Africa have a lower incidence of breast cancer than women in developed countries (age-standardised rate (ASR) of 36 vs 74) but a higher mortality rate (ASR of 17 vs 15). Deaths attributed to breast cancer were reported to be higher in LMICs than in more developed countries, with 324,000 versus 198,000 reported deaths, respectively (Ferlay 2015). One reason for this could be the ad-

vanced stage of disease at presentation. A study from Kenya reported that more than 60% of women with breast cancer received the diagnosis at disease stage III or IV (Sayed 2014). Similarly, almost 50% of women from four major hospitals in India presented with stage III and IV disease (Agarwal 2008), as was the case in a review and registry analysis of breast cancer trends in six Arab countries for which data regarding tumour stage were available (Saghir 2007). As cited by Saghir 2007, data from the National Cancer Institute of Cairo showed breast cancer stages III and IV to be around 80% to 90%. Similarly, most women from the four-hospital study in India (Agarwal 2008) presented with stage IIIB (35%), stage IIIA (27%) and stage IV (8% to 10%) disease, and only very few women (approximately 5%) presented with stage I disease. This late presentation of breast cancer may reflect lack of awareness about breast cancer among women and, in particular, little or no knowledge about early symptoms and signs and available screening and treatment options.

Various barriers at individual and community levels coupled with poorly functional health systems are likely contributing factors. Limited access to cancer screening and treatment facilities in remote areas, where most of the population of LMICs resides, may also contribute to late presentation of breast cancer. In addition, no national or population-based screening programmes for breast cancer are available in most LMICs, where mammography is too costly to implement and sustain. In addition, limited evidence is available on the role of mammography in reducing breast cancer mortality among women between 40 and 50 years of age (Lauby-Secretan 2015) - the age groups within which most cancers in LMICs are diagnosed (Knaul 2012). Even among health workers, knowledge and clinical skills related to screening, diagnosis and treatment of breast cancer are limited. As an example, survey results from Nigeria report that among 393 female health workers (102 doctors, 254 nurses and 37 radiographers, laboratory scientists and pharmacists), 55% of respondents had overall poor knowledge of breast cancer risk factors and furthermore, of the female respondents eligible for breast cancer screening only 3.1% had ever had a screening mammogram done (Akhigbe 2009). Clinical breast examination (CBE) is an inexpensive early detection technique for breast cancer for which sufficient evidence shows downstaging of disease at presentation (Lauby-Secretan 2015). However, health workers in LMICs may be inadequately trained to perform good quality CBEs and therefore are likely to dismiss breast complaints and to miss early disease, compounding the problem of late presentation. Although there is inadequate evidence to show that CBE reduces mortality from breast cancer (Lauby-Secretan 2015), the important issue in LMICs is early detection of breast cancer, rather than the search for subcentimetre tumours through screening mammography (Dey 2014). This review aims to explore different training methods/programmes in CBE for various groups of health workers and to determine whether training in CBE improves the quality of the technique and the ability of health workers to detect breast cancers early.

## Description of the intervention

Screening and early detection of breast cancer can provide maximum beneficial impact in lowering morbidity and mortality due to breast cancer (Dey 2014). It has been reported that between 1990 and 1998, an estimated 6.4% of the 21% decrease in mortality from breast cancer among women between 55 and 69 years of age in the United Kingdom was directly attributable to screening (Blanks 2000). The most widely adopted method of screening for breast cancer remains mammography. However, in most developing countries, constrained health infrastructure combined with limited trained personnel makes high-quality population-based mammographic screening programmes too costly to implement and sustain (Dey 2014). In LMICs, many breast cancers are diagnosed in women younger than 54 years of age (Knaul 2012), whose breasts are denser (Heng 2004), thus limiting the accuracy of mammographic diagnosis. The level of awareness among women of the utility of mammography as a screening tool for breast cancer is limited (Alharbi 2011; Obajimi 2013), and those who have heard of the tool often cite financial challenges as a limiting factor in accessing the service. As an example, in Ghana, a Knowledge Attitude and Practice (KAP) study suggested that 33.5% of respondents did not know of the existence of mammography services, and of those who were aware of such services, 27% cited financial reasons for not accessing mammography (Opoku 2012). American Cancer Society (ACS) guidelines (Smith 2013), which were recently updated (Oeffinger 2015), now state that CBE is currently not recommended in settings where mammography is available, but it is likely that CBE provides significantly greater benefit in settings where mammography is not available. It is noteworthy that most women in LMICs have neither regular general health exams nor access to good quality mammography, thus their only contact for a breast complaint might be a health worker within the community. Although the utility of CBE as a breast cancer screening and early detection tool has been mired in controversy (Larkin 2001), it is possible that CBE is being performed by health workers who have not been adequately trained in the correct technique. Training health workers in CBE and using these trained personnel to implement early detection programmes for breast cancer may provide the only opportunity for women in LMICs to undergo regular breast examination for early detection of breast cancer.

CBE is a systematic method that involves physical examination of the breast by a health worker (NCB Dictionary). Its main purpose is to detect breast abnormalities for onward referral to the next level of care. Various techniques can be used to train diverse groups of health workers in CBE. The main considerations for a standard CBE include clinical history, visual inspection, palpation and interpretation and reporting of findings (Saslow 2004). Some techniques such as using silicone breast models and adopting objective structured clinical examination training tools have been reported to increase the sensitivity of the tool (Saslow 2004). Task shifting involves training community health workers (CHWs) in CBE by

using role modelling to empower them to detect breast cancer at an earlier disease stage (Wadler 2011). A competency-based training programme for primary care physicians and nurses in breast health care that combines technical knowledge, skills and behaviours has been proposed to circumvent the shortage of specialist personnel in LMICs (Harford 2008). Training community nurses to implement a combination of breast self-examination (BSE) and CBE was shown to downstage breast cancer presentation in the Cairo Breast Screening Trial (Miller 2008). Interim results from a cluster-randomised controlled trial showed that training primary health workers for a specified duration of time in CBE, on the basis of the modified Canadian Breast Screening protocol, and implementing the CBE programme as provided by trained health-care personnel resulted in downstaging of breast cancer presentation (Mittra 2010). Preliminary results of another randomised controlled trial (RCT) from India show that upon completion of a structured three-week training programme in CBE that targeted female health workers with a tertiary level of education, a significant number of early breast cancers were detected in the intervention arm when compared with the control arm (Sankaranarayanan 2011). This contrasts with results from four Canadian organised breast cancer screening programmes, which showed that use of trained health workers in CBE contributed little to early detection of breast cancer (Bancej 2003). Similarly, a trial in the Philippines (Pisani 2006) failed to demonstrate any benefit for downstaging of breast cancer after nurses were trained in CBE. This is one important reason for the controversy surrounding CBE in LMICs. In particular, the sensitivity of CBEs performed by nurses is low, supporting our premise that the quality of CBE performed may be an issue.

### How the intervention might work

The Breast Health Global Initiative (BHGI), established in 2002, is an international health alliance that develops evidence-based and resource-sensitive guidelines for screening, early detection, diagnosis and treatment of breast cancer in LMICs. According to its recommended guidelines for breast cancer, screening should be adopted within the local context and should take into account available resources, with a view towards encouraging incremental improvements ultimately leading to an ideal healthcare delivery system (Smith 2006; Yip 2008). This would offer a more sustainable approach for early detection of breast cancer in LMICs. Breast self-awareness (BSA) education and CBE may be important techniques for early detection of breast cancer in the LMIC setting. Given that a large proportion of disease is diagnosed at late stages (Dey 2014), care providers have a great opportunity to make a difference in breast cancer mortality through earlier detection of palpable masses, which can be attained by training a broad group of health workers working within communities, including nurses and CHWs.

CBE remains a viable option for detection of breast cancer at an early stage, when the disease is potentially curable. CBE is a simple procedure that can be performed by a health worker at any level of a healthcare facility, and, if appropriately performed, it can detect lumps when they are still small and can contribute to early detection and probably reduced morbidity and mortality from breast cancer. In addition, health workers can be trained in screening CBE or evaluation of breast masses. Screening or evaluation could take place in facilities or in patients' homes, as was demonstrated in a pilot study from Sudan (Abuidris 2013). Performance of a CBE also provides an opportunity for the health worker to educate women on breast self-awareness and breast health care (Farid 2014). The CBE programme can be integrated into existing training programmes for community health workers, such as Visual Inspection by Acetic Acid (VIA) for cervical cancer screening, as has been described in a Malaysian trial (Devi 2007). The CBE method can be used as an opportunistic early detection tool by a trained health worker when women present at a health facility for other problems, or it can be included as a component of population-based screening and early detection programmes through integration into existing women's reproductive health programmes (Farid 2014). Through refresher training of CHWs in CBE, the programme can become a sustainable low-cost model for embedding early detection of breast cancer into LMICs (Wadler 2011).

### Why it is important to do this review

Any improvement in breast cancer outcomes requires creating awareness, providing access to early detection, making an accurate diagnosis, referring patients appropriately and maintaining the proper standard of treatment. Training health workers in CBE for early detection of breast cancer is an important concept for promoting breast health. It has the potential to promote early detection of breast cancer in the developing world, where mammography is limited and inaccessible for most women. Although controversy surrounds the utility of CBE as a mass breast screening tool (Larkin 2001), with large RCTs in China and Russia (Kösters 2003; Thomas 1997) showing no benefit for mortality from breast cancer when BSE or CBE is performed in isolation, evidence showing the efficacy of training health workers in CBE as an early detection tool in the developing world is limited. An RCT from the Philippines (Pisani 2006) that studied clinical outcomes of CBE performed by trained nurses had to be abandoned owing to participant non-compliance with follow-up and treatment guidelines. This RCT reported that despite training of nurses, both inexperience of the health worker and breast cancer beliefs and behaviours at the individual level contributed to the low sensitivity (53.2%) of the programme, and that these concerns must be addressed before future screening programmes are implemented. Work from other health disciplines on the effectiveness of training health workers to improve care has been previously published. A recently updated Cochrane review of in-service neonatal emer-

gency care courses for nurses (Opiyo 2015) reported that although evidence of the effectiveness of training for neonatal mortality was inconclusive, the two trials included in the review provided evidence of moderate certainty indicating that newborn resuscitation training compared with usual care improved provider performance of appropriate resuscitation (trained 66% vs usual care 27%, risk ratio 2.45, 95% confidence interval 1.75 to 3.42). In addition, evidence of moderate quality suggested that training of nurses reduced inappropriate resuscitation and in the short term improved healthcare professionals' treatment of seriously ill babies (Opiyo 2015).

Within the context of knowledge, experience and recommendations from global practitioners, it is recognised that community engagement is key to strengthening interventions that improve health outcomes. In particular, community-based interventions have been recognised as playing an important role in improving maternal, newborn and child health (Rifkin 2014). Community-based health workers are "strategically placed to facilitate community participation and stimulate critical thinking; and they act as a catalyst to social action to address the social and cultural determinants of poor health" (Perry 2009). Training CHWs and other health workers in CBE for early detection of breast cancer can therefore provide a sustainable model in the LMIC setting, where existing health infrastructure and resources are overwhelmed by management of diseases of infective origin. A review of breast cancer control in South Africa (Wadler 2011) recommended that, on the basis of low cost and minimal skills training, CBE can be implemented in an LMIC setting by training CHWs and by integrating breast health care into existing primary healthcare programmes. However, the authors admit that the pragmatic success of implementing trained CHW breast screening activities requires good quality evidence derived from RCTs.

## OBJECTIVES

To assess whether training in CBE improves the ability of health workers in LMICs to detect early breast cancer.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomised controlled trials (RCTs) (including individual and cluster-randomised trials) and quasi-experimental studies. If we identify no RCTs, we will consider controlled before-and-after (CBA) studies.

#### Types of participants

We will include training of any group of health workers (including lay and professional health workers) to perform CBE in community settings for women aged 18 years and older. Community settings will include home visitations and visits to basic primary healthcare centres.

#### Types of interventions

##### Intervention

Any form of training provided to any group of health workers (lay or professional) to conduct CBE as an opportunistic or population-based early detection tool for breast cancer in community settings in LMICs (as defined by World Bank classification).

##### Comparator

No training of health workers in CBE or use of any other mass screening or early detection tools for breast cancer (breast self-examination, ultrasonography, mammography or magnetic resonance imaging).

#### Types of outcome measures

##### Primary outcomes

- Breast cancer stage at the time of presentation: defined as the proportion of women with breast cancer diagnosed at each stage. We will dichotomise breast cancer into early and late stages. We will define early stage as breast cancer that has not spread beyond the breast or the axillary lymph nodes, including ductal carcinoma in situ and stages I, IIA, IIB and IIIA breast cancers; we will define late stage as breast cancer at stages IIIB and IV (NCB Dictionary). The numerator will represent the proportion of women with a diagnosis of early or late breast cancer among the total number of women given a cancer diagnosis

##### Secondary outcomes

- Knowledge attitude and practice (KAP) outcomes - defined as the KAP of breast cancer screening - early detection and diagnosis among health workers and women within communities. We will report KAP as described by study authors as ordinal or continuous outcomes on a scale, depending on what has been reported in the primary study (e.g. the number of correct answers on a questionnaire on knowledge related to CBE, the extent of current knowledge and practice in performing the CBE)

- Accuracy of health worker-performed CBE (e.g. sensitivity and specificity, positive predictive value, performance on checklists, performance as defined by individual study authors)
  - CBE coverage: defined as the proportion of the population covered by CBE interventions (intervention group) of the total eligible study population, as defined by respective study authors. The denominator for CBE coverage will represent women at risk (the population of women of reproductive age in the study area), and the numerator will represent those who actually experienced CBE
  - Follow-up: defined as the proportion of women who completed follow-up after screening and CBE and advice to complete follow-up
  - Breast cancer mortality: defined as deaths among women who received a diagnosis of breast cancer
  - Cost-effectiveness: defined as relative costs and outcomes of training health workers in CBE. This information will be reported as described by study authors

We will assess the quality of evidence for inclusion in the 'Summary of findings' table for the following outcomes.

- Breast cancer stage at the time of presentation.
- Accuracy of health worker-performed CBE.
- Completion of follow-up.

## Search methods for identification of studies

### Electronic searches

We will search the following databases.

- The Cochrane Breast Cancer Group (CBCG) Specialised Register. Details of search strategies used by the Group to identify studies and of the procedure used to code references are provided in the Group module (<http://www.mrw.interscience.wiley.com/cochrane/clabout/articles/BREASTCA/frame.html>). We will extract the key words “breast cancer screening, early detection and diagnosis, low and middle income countries, resource challenged/constrained settings, community screening, clinical breast exam, self breast exam, breast self examination, ultrasound exam, mammography, mass screening, population based screening, opportunistic screening, training in clinical breast exam, community health workers training” and will consider identified studies for inclusion in the review.
  - The Cochrane Central Register of Controlled Trials (CENTRAL; latest issue) in the Cochrane Library ([Appendix 1](#)).
  - MEDLINE (via OvidSP; from 1946 to present; [Appendix 2](#)).
  - Embase (via OvidSP; from 1974 to present; [Appendix 3](#)).
  - The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (<http://apps.who.int/trialsearch/Default.aspx>) for all prospectively registered and ongoing trials ([Appendix 4](#)).

- Clinicaltrials.gov (<http://clinicaltrials.gov/>; [Appendix 5](#)).

## Searching other resources

### Bibliographic searching

We will try to identify additional studies from reference lists of identified relevant trials or reviews. We will obtain a copy of the full article for each reference reporting a potentially eligible trial. When this is not possible, we will attempt to contact study authors to obtain required information.

## Data collection and analysis

### Selection of studies

Two review authors (SS and PO) will independently assess all studies identified for possible inclusion as a result of the search. We will resolve disagreements through discussion or, if required, through consultation with a third review author (AN). We will obtain a copy of the full article for each reference reporting a potentially eligible trial. When this is not possible, we will attempt to contact study authors to request additional information. When data are limited, or when information on study methods is not provided, we will request further information from the study authors. We will include relevant articles published in all languages. We will attempt to obtain translated versions of the included articles written in languages other than English. We will record excluded trials in the 'Characteristics of excluded studies' table along with reasons for their exclusion.

### Data extraction and management

Two review authors (PO and ASM) will extract data independently, using a predesigned data extraction form. We will resolve discrepancies through discussion, or, if required, we will consult with a third review author (RAS). We will request further information from study authors if extracted data are limited. For studies with more than one publication, we will extract data from all publications but will consider the final or updated version of each study as the primary reference.

We will extract the following information from the included studies.

- Publication details (i.e. year, country, study authors).
- Methods (i.e. study design, location/setting, follow-up period).
- Participants (i.e. age).
- Interventions (i.e. CBE training duration, type, frequency, trainers).
- Outcomes reported by study authors.

We will enter information related to the included studies into Review Manager software (RevMan). When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to obtain further details.

### **Assessment of risk of bias in included studies**

Two review authors (SS and RAS) will independently assess risk of bias for each RCT using the Cochrane 'Risk of bias' tool described in Higgins 2011. For non-randomised studies, we will assess risk of bias using the Cochrane 'Risk of bias In non-randomised studies of interventions' (ROBINS-I) assessment tool. We will resolve disagreements by discussion or by consultation with a third review author (AN).

### **Cochrane 'Risk of bias' tool for RCTs**

#### **Random sequence generation (checking for possible selection bias)**

For each included study, we will describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether this method should produce comparable groups. We will assess each method as:

- low risk of bias (any truly random process, e.g. random number table, computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth, hospital or clinic record number); or
- unclear risk of bias.

#### **Allocation concealment (checking for possible selection bias)**

We will describe for each included study the method used to conceal allocation to interventions before assignment and will assess whether intervention allocation could have been foreseen in advance of, or during, recruitment, or changed after assignment. We will assess each method as:

- low risk of bias (e.g. telephone or central randomisation, consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation, unsealed or non-opaque envelopes, alternation, date of birth); or
- unclear risk of bias.

#### **Blinding of participants and personnel (checking for possible performance bias)**

For each included study, we will describe the method used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that lack of blinding would be unlikely to affect results. We will assess

blinding separately for different outcomes or classes of outcomes.

We will assess each method as:

- low, high or unclear risk of bias for participants; and
- low, high or unclear risk of bias for personnel.

#### **Blinding of outcome assessment (checking for possible detection bias)**

We will describe for each included study methods used, if any, to blind outcome assessors to knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or classes of outcomes. We will assess methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

#### **Incomplete outcome data (checking for possible attrition bias due to the quantity, nature and handling of incomplete outcome data)**

For each included study, and for each outcome or class of outcomes, we will describe completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported and will provide the numbers included in the analysis at each stage (compared with the total number of randomised participants), reasons for attrition or exclusion when reported and whether missing data were balanced across groups or were related to outcomes. When sufficient information is reported, or can be supplied by study authors, we will re-include missing data in the analyses that we undertake. We will assess each method as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation); or
- unclear risk of bias.

#### **Selective reporting (checking for reporting bias)**

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We will assess each method as:

- low risk of bias (when it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (when not all of the study's prespecified outcomes have been reported; when one or more reported primary outcomes were not prespecified; when outcomes of interest are reported incompletely and so cannot be used; when the study fails to include results of a key outcome that would have been expected to have been reported); or
- unclear risk of bias.



## Other bias

We will describe for each included study any important concerns that we have about other possible sources of bias. We will assess whether each study was free of other problems that could put it at risk of bias and will judge each study as follows.

- Low risk of other bias.
- High risk of other bias.
- Unclear whether risk of other bias is present.

For cluster-randomised trials, we will additionally assess the following.

- Recruitment bias.
- Baseline imbalance.
- Loss of clusters.
- Incorrect analysis.
- Comparability with individually randomised trials.

For non-randomised studies, we will use the Cochrane 'Risk of bias In non-randomised studies of interventions' (ROBINS-I) assessment tool to assess bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviation from intended interventions, bias due to missing data, bias in measurement of outcomes and bias in selection of the reported result.

## Cochrane 'Risk of bias' tool for non-randomised studies

Potential confounders and co-interventions that could be different between intervention groups include education status, socioeconomic status, access to a health facility, availability and level of skill of health workers and concurrent healthcare campaigns pertaining to breast cancer awareness besides the intervention of interest.

## Bias due to confounding

A confounding domain is a pre-intervention prognostic factor that predicts whether an individual receives one or the other intervention of interest. We will report this as follows.

- Low risk of bias: The study is comparable with a well-performed randomised trial with regard to this domain.
- Moderate risk of bias: The study is sound for a non-randomised study with regard to this domain but cannot be considered comparable with a well-performed randomised trial.
- Serious risk of bias: The study has some important problems.
- Critical risk of bias: The study is too problematic to provide any useful evidence on effects of the intervention.
- No information is provided on which to base a judgement about risk of bias for this domain.

## Bias in selection of participants into the study

Selection bias occurs when some eligible participants or initial follow-up time of some participants or some outcome events are

excluded in a way that leads to a different association between intervention and outcome than would have been observed in the target trial. We will report this as follows.

- Low risk of bias: The study is comparable with a well-performed randomised trial with regard to this domain.
- Moderate risk of bias: The study is sound for a non-randomised study with regard to this domain but cannot be considered comparable with a well-performed randomised trial.
- Serious risk of bias: The study has some important problems.
- Critical risk of bias: The study is too problematic to provide any useful evidence on effects of the intervention.
- No information is provided on which to base a judgement about risk of bias for this domain.

## Bias in classification of interventions

Bias may be introduced if intervention status is misclassified. This is seldom a problem in randomised trials and other experimental studies because interventions are actively assigned by the researcher, and their accurate recording is a key feature of the study. However, in observational studies, information about interventions allocated or received needs to be collected. We will report this as follows.

- Low risk of bias: The study is comparable with a well-performed randomised trial with regard to this domain.
- Moderate risk of bias: The study is sound for a non-randomised study with regard to this domain but cannot be considered comparable with a well-performed randomised trial.
- Serious risk of bias: The study has some important problems.
- Critical risk of bias: The study is too problematic to provide any useful evidence on effects of the intervention.
- No information is provided on which to base a judgement about risk of bias for this domain.

## Bias due to deviations from intended interventions

This domain of biases arises when systematic differences exist between the care provided to experimental intervention and comparator groups, beyond assigned interventions. We will report this as follows.

- Low risk of bias: The study is comparable with a well-performed randomised trial with regard to this domain.
- Moderate risk of bias: The study is sound for a non-randomised study with regard to this domain but cannot be considered comparable with a well-performed randomised trial.
- Serious risk of bias: The study has some important problems.
- Critical risk of bias: The study is too problematic to provide any useful evidence on effects of the intervention.
- No information is provided on which to base a judgement about risk of bias for this domain.

### **Bias due to missing data**

Among other reasons, missing data may arise through attrition (loss to follow-up), missed appointments, incomplete data collection and exclusion of participants from analysis by primary investigators. We will report this as follows.

- Low risk of bias: The study is comparable with a well-performed randomised trial with regard to this domain.
- Moderate risk of bias: The study is sound for a non-randomised study with regard to this domain but cannot be considered comparable with a well-performed randomised trial.
- Serious risk of bias: The study has some important problems.
- Critical risk of bias: The study is too problematic to provide any useful evidence on effects of the intervention.
- No information is provided on which to base a judgement about risk of bias for this domain.

### **Bias in measurement of outcomes**

Bias may be introduced if outcomes are misclassified or are measured with error. We will report this as follows.

- Low risk of bias: The study is comparable with a well-performed randomised trial with regard to this domain.
- Moderate risk of bias: The study is sound for a non-randomised study with regard to this domain but cannot be considered comparable with a well-performed randomised trial.
- Serious risk of bias: The study has some important problems.
- Critical risk of bias: The study is too problematic to provide any useful evidence on effects of the intervention.
- No information is provided on which to base a judgement about risk of bias for this domain.

### **Bias in selection of the reported result**

Outcome reporting bias (ORB) arises when the outcome domain is not reported or is partially reported on the basis of direction, magnitude or statistical significance of its association with the intervention group. We will report this as follows.

- Low risk of bias: The study is comparable with a well-performed randomised trial with regard to this domain.
- Moderate risk of bias: The study is sound for a non-randomised study with regard to this domain but cannot be considered comparable with a well-performed randomised trial.
- Serious risk of bias: The study has some important problems.
- Critical risk of bias: The study is too problematic to provide any useful evidence on effects of the intervention.
- No information is provided on which to base a judgement about risk of bias for this domain.

### **Overall risk of bias**

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in [Higgins 2011](#). We will assess the likely magnitude and direction of bias, and whether we consider bias is likely to have an impact on study findings. We will explore the impact of the level of bias by undertaking sensitivity analyses.

### **Measures of treatment effect**

#### **Dichotomous data**

We will report dichotomous outcomes (e.g. breast cancer mortality; stage at presentation; knowledge attitude and practice outcomes; accuracy of performance; CBE coverage; follow-up) as risk ratios (RRs) and risk differences (RDs) with 95% confidence intervals (CIs). We will pool data for meta-analysis using the pooled log-RR, when appropriate.

#### **Continuous data**

For continuous data, we will use the mean difference (MD) if outcomes are measured in the same way between studies. We will use the standardised mean difference (SMD) to combine studies that measure the same outcome with 95% CIs while using different scales.

### **Unit of analysis issues**

#### **Cluster-RCTs**

We will include in the analyses cluster-RCTs along with individual RCTs. We will adjust standard errors according to the methods described in [Higgins 2011](#) by using an estimate of the intracluster correlation coefficient (ICC) derived from the study (if possible), from a similar study or from a study of a similar population. If we use ICCs from other sources, we will report this and will conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-RCTs and individual RCTs, we plan to synthesise relevant information. We will consider it reasonable to combine results from both if we note little heterogeneity between study designs, and if the interaction between effects of the intervention and choice of randomisation unit is considered unlikely. We will acknowledge heterogeneity in the randomisation unit and will perform a sensitivity analysis to investigate its effects.

### Studies with more than two intervention groups

If we identify studies with more than two intervention groups (multi-arm studies), we will combine groups when possible to create a single pair-wise comparison or will use the methods set out in [Higgins 2011](#) to avoid double-counting of study participants. For subgroup analyses, when the control group is shared by two or more study arms, we will divide the control group (events and total population) over the number of relevant subgroups to avoid double-counting of participants.

### Dealing with missing data

We will describe missing data, including the number of participants lost to follow-up. Differential dropout rates can lead to biased estimates of effect size, and bias may arise if the reasons for dropping out differ across groups. We shall report the reasons for loss to follow-up. If data are missing for some cases, or if reasons are not reported, we will contact the study authors. For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by performing sensitivity analysis. As far as possible, we will perform analyses on an intention-to-treat basis for all outcomes, that is, we will attempt to include in the analysis all participants randomised to each group, and we will analyse all participants in the group to which they were allocated, regardless of whether they received the allocated intervention. The denominator for each outcome in each study will be the number randomised minus the number of participants whose outcomes are known to be missing.

### Assessment of heterogeneity

We will examine included studies for clinical, methodological and statistical heterogeneity. We shall assess clinical heterogeneity by comparing the distribution of important factors, such as study participants, study setting, dose, assessment tools and duration of the intervention and of co-interventions. We shall evaluate methodological heterogeneity on the basis of factors such as method of sequence generation, allocation concealment, blinding of outcome assessment and losses to follow-up. We will assess statistical heterogeneity in each meta-analysis using  $\tau^2$ ,  $I^2$  and  $\text{Chi}^2$  statistics. We will regard heterogeneity as substantial if  $I^2$  is greater than 50%, and if  $\tau^2$  is greater than zero or the P value is low ( $< 0.10$ ) in the  $\text{Chi}^2$  test for heterogeneity. The importance of the observed value of  $I^2$  depends on (1) magnitude and direction of effects and (2) strength of evidence for heterogeneity. A rough guide for the  $I^2$  statistic follows.

- 0% to 40%: might not be important.
- 30% to 60%: may represent moderate heterogeneity.
- 50% to 90%: may represent substantial heterogeneity.
- 75% to 100%: shows considerable heterogeneity.

### Assessment of reporting biases

If 10 or more studies are included in the meta-analysis, we will investigate reporting biases (such as publication bias) by using funnel plots. We will assess funnel plot asymmetry visually and with the use of formal tests. For continuous outcomes, we will use the test proposed by [Egger 1997](#). For dichotomous outcomes, we will use the test proposed by [Harbord 2006](#). If asymmetry is detected in any of these tests or is suggested by a visual assessment, we will attempt to explore contextual factors, including the plausibility of publication bias as an explanation for the asymmetry, and we will compare fixed-effect and random-effects estimates of the intervention effect when we observe heterogeneity between studies ([Higgins 2011](#); [Sterne 2011](#)).

### Data synthesis

We will perform statistical analysis using [RevMan](#). We will use fixed-effect meta-analysis in combining data when it is reasonable to assume that studies are estimating the same underlying treatment effect, that is, when studies are examining the same intervention, and that study populations and methods are judged to be sufficiently similar. If clinical heterogeneity is sufficient to suggest that underlying treatment effects differ between studies, and if we detect substantial statistical heterogeneity, we will use random-effects meta-analysis to produce an overall summary.

For continuous outcomes, we will combine data using the inverse variance method on the mean difference scale. For the random-effects model, which incorporates an assumption that different studies are estimating different, yet related, intervention effects, we will use the DerSimonian and Laird method. For dichotomous outcomes, we will combine data on the log-RR scale using the Mantel-Haenszel method.

We will set out the main findings of the review in 'Summary of findings' tables prepared via the GRADE approach ([Guyatt 2008](#)) with [GRADEpro 2014](#) software. We will list the primary outcome for each comparison with estimates of relative effects along with the numbers of participants and studies contributing data for those outcomes. For each individual outcome, we shall assess the quality of the evidence using the GRADE approach, which involves consideration of within-study risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias. We will rate the quality of the body of evidence for each key outcome as 'high', 'moderate', 'low' or 'very low'.

### Subgroup analysis and investigation of heterogeneity

We will perform subgroup analysis according to the following.

- Types of health workers (nurses, physicians, lay health workers, etc).
- Duration of training (as reported by study authors).

## Sensitivity analysis

We will perform sensitivity analyses to examine the effect of removing studies at high risk of bias (those with high or unclear risk of bias according to method and adequacy of allocation concealment; blinding status of participants; percentage lost to follow-up or attrition of 20%; and a random-effects model of the primary analysis). We will also perform sensitivity analyses to examine different types of study designs and different ICC values.

## ACKNOWLEDGEMENTS

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- \* Indicates the major publication for the study

## APPENDICES

### Appendix I. CENTRAL

- #1 MeSH descriptor: [Community Health Workers] explode all trees  
 #2 MeSH descriptor: [Health Personnel] explode all trees  
 #3 (health worker\* or health care worker\* or health professional or health personnel or doctor\* or nurse\* or physician\*)  
 #4 #1 or #2 or #3  
 #5 MeSH descriptor: [Health Education] explode all trees  
 #6 MeSH descriptor: [Education, Continuing] explode all trees  
 #7 MeSH descriptor: [Education, Medical] explode all trees  
 #8 MeSH descriptor: [Education, Nursing] explode all trees  
 #9 (train\* or training or education or curriculum or teaching or learning or staff development or medicine)  
 #10 #5 or #6 or #7 or #8 or #9  
 #11 #4 and #10  
 #12 MeSH descriptor: [Health Knowledge, Attitudes, Practice] explode all trees  
 #13 #11 or #12  
 #14 MeSH descriptor: [Physical Examination] explode all trees  
 #15 ((physical or clinical breast or clinical or breast) adj1 exam\*)  
 #16 clinical breast examination  
 #17 MeSH descriptor: [Mass Screening] explode all trees  
 #18 #14 or #15 or #16 or #17  
 #19 MeSH descriptor: [Breast Neoplasms] explode all trees

#20 breast near neoplasm\*  
 #21 breast near carcinom\*  
 #22 breast near cancer\*  
 #23 breast near tumour\*  
 #24 breast near tumor\*  
 #25 breast near malignan\*  
 #26 #19 or #20 or #21 or #22 or #23 or #24 or #25  
 #27 #13 and #18 and #26

## Appendix 2. MEDLINE via OvidSP

##The proposed search strategies below have been developed for you. Please review the strategies below to make sure that all search terms have been included.##

1	exp Community Health Workers/
2	exp Health Personnel/
3	community health worker*.tw.
4	(health worker* or health care worker* or health professional or health personnel or doctor* or nurse* or physician*).tw
5	1 or 2 or 3 or 4
6	exp Health Education/
7	exp Education, Continuing/
8	exp Education, Medical/
9	exp Education, Nursing/
10	(train* or training or education or curriculum or teaching or learning or staff development or medicine).tw
11	6 or 7 or 8 or 9 or 10
12	5 and 11
13	exp Community Health Workers/ed [Education]
14	exp Health Knowledge, Attitudes, Practice/
15	exp Health Personnel/ed [Education]
16	12 or 13 or 14 or 15
17	exp Physical Examination/mt [Methods]
18	((physical or clinical breast or clinical or breast) adj1 exam*).tw

(Continued)

19	clinical breast examination.tw.
20	exp Mass Screening/mt [Methods]
21	17 or 18 or 19 or 20
22	exp Breast Neoplasms/
23	(breast adj6 cancer\$.tw.
24	(breast adj6 neoplasm\$.tw.
25	(breast adj6 carcinoma\$.tw.
26	(breast adj6 tumor\$.tw.
27	or/22-26
28	16 and 21 and 27
29	Animals/ not Humans/
30	28 not 29

### Appendix 3. Embase via OvidSP

1	exp health auxiliary/
2	exp health care personnel/
3	community health worker*.tw.
4	(health worker* or health care worker* or health professional or health personnel or doctor* or nurse* or physician*).tw
5	1 or 2 or 3 or 4
6	exp medical education/
7	exp continuing education/
8	exp nursing education/
9	(train* or training or education or curriculum or teaching or learning or staff development or medicine).tw



(Continued)

10	6 or 7 or 8 or 9
11	5 and 10
12	exp physical examination/
13	((physical or clinical breast or clinical or breast) adj1 exam*).tw
14	clinical breast examination*.tw.
15	exp mass screening/
16	12 or 13 or 14 or 15
17	exp breast/
18	exp breast disease/
19	(17 or 18) and exp neoplasm/
20	exp breast tumor/
21	exp breast cancer/
22	exp breast carcinoma/
23	(breast\$ adj5 (neoplas\$ or cancer\$ or carcin\$ or tumo\$ or metasta\$ or malig\$)).ti,ab
24	19 or 20 or 21 or 22 or 23
25	11 and 16 and 24
26	limit 25 to (human and embase)

#### Appendix 4. WHO ICTRP search portal

Basic search:

1. Clinical breast examination
2. Clinical breast examination AND education

Advanced search:

1. Condition: clinical breast examination

Intervention: nurse OR worker OR teach OR education OR lay OR community

Recruitment status: All

2. Condition: clinical breast examination AND breast cancer

Intervention: nurse OR worker OR teach OR education OR lay OR community

Recruitment status: All

3. Condition: breast cancer

Intervention: clinical breast examination

Recruitment status: All

## Appendix 5. ClinicalTrials.gov

Basic search:

1. Clinical breast examination
2. Clinical breast examination AND education
3. clinical breast examination AND (health worker OR nurse OR lay OR community)

Advanced search:

1. Conditions: clinical breast examination

Interventions: education OR train\* OR health worker OR nurse OR lay OR community

Recruitment: All studies

2. Conditions: Breast cancer\* OR breast neoplasm\* OR breast carcinoma\*

Interventions: (education OR train\* OR health worker OR nurse OR lay OR community) AND clinical breast examination

Recruitment: All studies

## CONTRIBUTIONS OF AUTHORS

- Drafted the protocol: RAS, SS, AN, PO, ASM.
- Selected studies: SS, PO, RAS.
- Extracted data from studies: PO, ASM, SS.
- Entered data into [RevMan](#): ASM, PO, SS, AN.
- Carries out the analysis: RAS, AN.
- Interpreted the analysis: RAS, AN, SS, ASM.
- Drafted the final review: RAS, SS, AN.
- Resolved disagreements: RAS, SS, AN.
- Updated the review: RAS, SS.

## DECLARATIONS OF INTEREST

SS: none known.

AN: none known.

PO: none known.

ASM: none known.

RAS: none known.