Appendix 2: Original protocol [posted as supplied by author]

What is the frequency of adverse event reporting in cancer screening trials: a literature survey

Background:

The idea that cancer screening may also lead to harm is not new but is increasingly recognized. (1–3) A number of concept papers, editorials and policy documents mention types of screen-related adverse events.(3,4,10,11,13,38–42) From them it is possible to draw some main ideas. Screening-related harm includes somatic and psychological adverse events.(4,7–13,42) These may result not only of the screening test but also from all the downstream investigations and therapies.(3,12,13,42) The importance of reporting adequately screening-related adverse events is supported by two main arguments. The first is that interventions where the benefits are modest or uncertain should merit detailed consideration of harms.(27) And indeed, systematic reviews of randomized trials of screening have shown, at best, modest improvements on mortality.(28,43) The second arises from the ethical specificities of screening. Screening is offered to healthy participants, and that offer is commonly unsolicited (meaning that screening is initiated by the healthcare system and not by the participant). Although a population benefit is expected, it is impossible to foresee whether a specific individual will have benefit or be harmed. This means that, the benefit for some will come at the expense of harm to others.(31–33)

It has been argued that the minimal evidence required to assess harms of screening includes the frequency and experiences of people with false positives, the frequency and experiences of people with overdiagnosis, and the frequency and severity of harms of workup and treatment.(13) Additionally, a number of authors distinguish explicitly psychological from somatic adverse events. (12,42) The number of invasive procedures can be a surrogate measure of somatic harm. Withdrawals due to adverse events of interventions are a proxy measure of severe adverse events.(19) False-negatives are considered an important contributor to screening-related harm when they lead to dismissal of cancer symptoms or when they lead to distrust in the health-care system.(7,10,41,44) However, it may be very difficult to assess when false negatives lead to symptom dismissal or distrust.

When reported, adverse events should be adequately defined. For each trial arm they should reported in absolute numbers or rates with separate reporting of at least the severe and life-threatening events.(19) However, this is not straight-forward for screening harms. First, it may be licit to assume that false positives and overdiagnosis can only occur in the intervention arm. Second, in some study designs, controls were unaware that they were part of a trial.(45–47) Therefore, there may be limited information about adverse events in the controls. Third, there is no accepted way of rating false positives for severity. It may be reasonable to assume that overdiagnosis is always severe as it implies invasive therapy and possibly radio- or chemo-therapy. It may also be possible to use severity grading scales such as the Common Terminology Criteria for Adverse Events to rate somatic and psychological adverse events.(48) But it seems clear that for each adverse event category it is possible to define screening adverse events and present absolute numbers for at least the intervention arm.

Before the implementation of organized screening, most authorities now require demonstration of mortality benefit in randomized trials. It is known that properly conducted and reported, randomized trials can offer high quality evidence on expected, common harms.(14,15) However, harms generally are poorly reported in randomized trials,(16–26) and there is limited evidence that reporting is worse in non-pharmacological trials than in drug trials. (22–24) Estimates of false positives and overdiagnosis do not require data beyond what is routinely collected in randomized trials of screening. Before a screening programme is implemented, there is already knowledge about the complications that may arise from diagnostic and therapeutic procedures. Thus, it is possible that adverse event reporting in cancer screening trials is better than for other medical technologies. To our knowledge, no study was ever conducted for harm reporting in screening. Hence, a literature survey of adverse event reporting in cancer screening trials will be conducted.

Objective:

To assess the frequency reporting of specific expected adverse events in a sample of randomized trials of cancer screening.

Methods

Protocol registration:

N/A

Eligibility criteria:

- Participants: Participants in cancer screening trials.
- Intervention: Breast cancer screening with mammography, self-examination or clinical examination; colorectal cancer screening with fæcal occult blood testing, fibrosigmoidoscopy, colonoscopy or virtual colonoscopy; lung cancer screening with chest X-ray or low-dose chest CT-scan; ovarian cancer screening with ultrasound and/or serological markers; prostate cancer screening with PSA; and other cancer screening technologies for which a Cochrane Systematic Review exists.
- Comparison: No screening or alternative cancer screening technology (active comparator).
- Outcomes: Reporting of overdiagnosis, reporting of false positives, reporting of induced somatic morbidity due to screening test or downstream procedures, reporting of induced psychological morbidity due to screening test or downstream procedures, reporting of the number of participants submitted to invasive procedures, reporting of withdrawals due to adverse events.
- Study design and methodological quality: Randomized trials where cancer screening is the single intervention being assessed, regardless of blinding status or trial dimension. Observational studies (including nested case controls, nested case series/ cohort studies), mathematical modelling studies (even if based on clinical trial data), studies that pool data from randomized trials and observational studies (when it is impossible to extract the randomized trial data separately), and letters, editorials or comments associated with randomized trial reports will be excluded.

Search methods for identification of sources:

Previous literature surveys of adverse event reports have varying degrees of search comprehensiveness. Some performed formal systematic reviews, using several databases, hand-searching strategies and contact with relevant researchers.(18,21) Others have restricted the survey to selected high-impact journals, under the assumption that these journals had more stringent reporting requirements that most journals.(20,24,26,49,50) A third strategy, that balances comprehensiveness and practicality, used the reference lists from previous systematic reviews.(19) When available, trial references will be abstracted from Cochrane Database of Systematic Reviews. Whenever a Cochrane systematic review does not exist, clinical trial reports will be sought through electronic literature search.

Cochrane systematic reviews

Search strategy for Cochrane systematic reviews:

We will search Cochrane Database of Systematic Reviews with the strategy ((“Mass Screening”[MeSH] exploding all subheadings AND Neoplasms[MeSH] exploding all subheadings) OR (screen* NEAR cancer)) through March 2012. Records will be limited to reviews but no other limits will be applied. The number of references obtained through database search, the number of potential relevant references which are selected for full text appraisal, references to be included in the analysis, and excluded references will be noted to create a PRISMA flow-chart.

Systematic review selection:

One reviewer will screen titles for potential relevant systematic reviews of effectiveness of cancer screening programmes. Only systematic reviews that have either disease specific mortality or total mortality as outcomes will be included. This means that systematic reviews of test accuracy and of interventions aimed at increasing participation will be excluded. Additionally, systematic reviews that only include observational studies will be also excluded.
Two reviewers will screen these references. Disagreements will be solved through consensus. Only original research reports will be included for abstraction of information on screening adverse events. No restriction to language or length of follow-up will be applied. This information will be added to the PRISMA flowchart.

Updating systematic review searches:

To identify potential new trials or trial reports for technologies assessed in systematic reviews, we will do an updated search. This search will replicate the strategy described in each of the selected systematic reviews for the Cochrane Central Register of Controlled Trials (The Cochrane Library, from inception until 31 May 2012).

Screening technologies without a Cochrane systematic review

Electronic searches

We will limit our electronic searches to the Cochrane Central Register of Controlled Trials (The Cochrane Library, from inception until 31 May 2012). Search strategies will use a combination of controlled vocabulary and free-text terms. There will be no language or publication status restrictions. The strategies will be composed of four dimensions: cancer-related terms, technology-related terms, screening-related terms and a randomized trial filter. Details of the search strategy are provided in the Appendix.

Grey literature, journals and conference proceedings, and other sources

Given that the aim is to assess the adequacy of harm reporting in clinical trials, no contact will be made with the study authors and no other sources of data will be sought.

Data collection and analysis:

Selection of studies

Two authors will scan titles and abstracts from the reference lists of Cochrane Systematic Reviews and from the electronic searches. When the title or abstract do not provide sufficient data to rule out eligibility, full text will be obtained and eligibility will be independently assessed by the same two authors. We will obtain full text of reports that fulfil the eligibility criteria. Disagreements will be solved through consensus. No restriction to language or length of follow-up will be applied. Then number and reasons for excluding a study will be recorded and added to the PRISMA flowchart.

Data extraction and management

Before information abstraction, one author will remove information about authors, affiliations, date of publication, journal, and references from all original research reports. For digital documents, this will be performed by covering this information with an opaque stamp and encrypting the .pdf file, so that commenting is allowed but moving objects in the document is not allowed. For print documents this will be performed by covering this information with a black marker and photocopying the document. Only copies will be distributed to the authors involved in abstracting the data.

A standardized extraction form with all variables will be developed. This extraction form will have two versions, one for studies retrieved through Cochrane Systematic Reviews and the other for studies retrieved through electronic searches. There will be a separate record for each selected publication. This means that, if a single publication reported two or more separate studies, then each study had an individual record. If the findings of a single study were spread across *n* publications, *n* records were obtained for each study. An identification tag will be attributed to each publication. Two authors will abstract the data for each study. The two records will be compared for data entry or coding errors. Disagreements will be solved through consensus.

Assessment of the risk of bias in individual studies:

N/A

Measures of treatment effect, unit of analysis, missing data, assessment of heterogeneity, assessment of reporting biases, data synthesis, subgroup analysis, sensitivity analysis, SoF table

N/A

Summary measures:

For references retrieved through Cochrane Systematic Reviews the following variables will be collected:

1. General characterization of the trial report
    1.1. Type of screening technology
    1.2. Year when the first participant was recruited
    1.3. Reporting of disease-specific mortality in the current report.
    1.4. Reporting of disease-specific incidence in the current report.
2. Outcomes
    2.1. Reporting of withdrawals due to negative experiences

2.2. Space devoted to harm reporting

2.3. Reporting of numerical estimate of

2.3.1. False positives

2.3.2. Overdiagnosis

2.3.3. Downstream somatic adverse events

2.3.4. Downstream psychological adverse events

2.3.5. Invasive procedures

2.3.6. Total mortality

Data items:

An automatic error checking mechanism will be built in the database used for data collections. If two raters assess the same entry differently, discrepancies between variables will be highlighted in a separate automatically generated report. Disagreements will be solved through consensus. To make this process easier, raters will be asked to record where the retrieved information was taken from the article.

Analysis plan

Categorical variables will be described with frequencies and percentages. Descriptive statistics (mean, standard deviation, median and interquartile range, extreme values) will be used for continuous variables. Data will be collected for three different hierarchal levels: cancer screening system, trial, publication. Data analysis will be conducted mostly at trial level.

Descriptive analysis plan

1. Prospective figure 1: Modified PRISMA flow-chart
2. Prospective figure 2: Bar chart presenting
    a. Group I (total)
        i. the absolute number of trials for that screening technology
    b. Group II (main outcomes)
        i. the absolute number of trials that report mortality reduction
        ii. the absolute number of trials that report incidence difference
    c. Group III (harmful outcomes)
        i. the absolute number of trials that report each of the 5 outcome variables
        ii. the absolute number of trials that report withdrawals due to negative experiences

3. Prospective figure 4: scatterplot year of publication and space devoted to harms (may give uninterpretable; there are papers that are entirely devoted to harms).

4. Text data

    a. Number of trials reporting any safety data (frequency) and data on each category of harm (frequency).

    b. Median of the space devoted to harm in each trial.

Explanatory analysis plan

Reporting of adverse events among different trials can be considered independent, whereas reporting of adverse events in the different publications of a same trial is likely to be related. Hence, explanatory data analysis will be conducted at the trial level.

Explanatory analysis will be limited by the number of included trials and by the number of events (reporting of a given adverse event). If possible, linear regression will be used for the space devoted to adverse event reporting and logistic regression for reporting of somatic adverse events and of reporting of false positives numeric estimates. If regression models are used, both univariate and multivariate models will be considered.

References

1. Brawley OW, Kramer BS. Cancer Screening in Theory and in Practice. Journal of Clinical Oncology. 2005 Jan 10;23(2):293–300.
2. Raffle A, Gray M. Screening: evidence and practice. Oxford; New York: Oxford University Press; 2007.
3. Croswell JM, Ransohoff DF, Kramer BS. Principles of cancer screening: lessons from history and study design issues. Semin. Oncol. 2010 Jun;37(3):202–15.
4. Black WC. Randomized Clinical Trials for Cancer Screening: Rationale and Design Considerations for Imaging Tests. Journal of Clinical Oncology. 2006 Jul 10;24(20):3252–60.
5. Woloshin S, Schwartz LM. The Benefits and Harms of Mammography Screening: Understanding the Trade-offs. JAMA: The Journal of the American Medical Association. 2010 Jan 12;303(2):164–5.
6. Welch HG, Woloshin S, Schwartz LM, Gordis L, Gøtzsche PC, Harris R, et al. Overstating the evidence for lung cancer screening: the International Early Lung Cancer Action Program (I-ELCAP) study. Arch. Intern. Med. 2007 Nov 26;167(21):2289–95.
7. EUnetHTA. Work Package 4. HTA Core Model for screening technologies - first public draft [Internet]. EUnetHTA; 2011 [cited 2012 Dec 24]. Available from: http://www.eunethta.eu/upload/WP4/Public%20consultation/HTA%20Core%20Model%20for%20screening_draft%20for%20public%20cons.pdf
8. Harris R, Sawaya GF, Moyer VA, Calonge N. Reconsidering the Criteria for Evaluating Proposed Screening Programs: Reflections From 4 Current and Former Members of the U.S. Preventive Services Task Force. Epidemiol Rev [Internet]. 2011 Jun 10 [cited 2011 Jul 5]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/21666224
9. Newman TB, Kohn MA. Screening tests. Evidence-based diagnosis. Cambridge;New York: Cambridge University Press; 2009. p. 116–37.
10. Holland W, Stewart S. Screening in disease prevention: what works? 1st ed. Oxford: Radcliffe; 2005.
11. Brodersen J, Jørgensen KJ, Gøtzsche PC. The benefits and harms of screening for cancer with a focus on breast screening. Pol. Arch. Med. Wewn. 2010 Mar;120(3):89–94.
12. Marshall KG. Prevention. How much harm? How much benefit? 2. Ten potential pitfalls in determining the clinical significance of benefits. CMAJ. 1996 Jun 15;154(12):1837–43.
13. Curry SJ, Byers T, Hewitt ME, National Cancer Policy Board (U.S.), editors. Potential of screening to reduce the burden of cancer. Fulfilling the potential of cancer prevention and early detection [Internet]. Washington, DC: National Academies Press; 2003 [cited 2012 Apr 2]. p. 156–223. Available from: http://search.ebscohost.com/login.aspx?direct=true&scope=site&db=nlebk&db=nlabk&AN=86985
14. Alibhai SMH. Cancer screening: The importance of outcome measures. Critical Reviews in Oncology/Hematology. 2006 Mar;57(3):215–24.
15. Irwig L, McCaffery K, Salkeld G, Bossuyt P. Informed choice for screening: implications for evaluation. BMJ. 2006 May 13;332(7550):1148–50.
16. Dans LF, Silvestre MAA, Dans AL. Trade-off between benefit and harm is crucial in health screening recommendations. Part I: general principles. J Clin Epidemiol. 2011 Mar;64(3):231–9.
17. Loke YK, Price D, Herxheimer A. Adverse effects. In: Higgins J, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions [Internet]. The Cochrane Collaboration; 2011 [cited 2011 Jul 26]. Available from: www.cochrane-handbook.org
18. Gøtzsche PC, Nielsen M. Screening for breast cancer with mammography. In: The Cochrane

Collaboration, Gøtzsche PC, editors. Cochrane Database of Systematic Reviews [Internet]. Chichester, UK: John Wiley & Sons, Ltd; 2011 [cited 2011 Jun 27]. Available from: http://doi.wiley.com/10.1002/14651858.CD001877.pub4
19. Hewitson P, Glasziou P, Irwig L, Towler B, Watson E. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. Cochrane Database Syst Rev. 2007;(1):CD001216.
20. Levin B, Prorok PC, Schottenfeld D, Fraumeni JF, editors. Principles of screening. Cancer Epidemiology and Prevention [Internet]. Oxford University Press; 2006 [cited 2012 Apr 2]. Available from: http://www.oxfordscholarship.com/view/10.1093/acprof:oso/9780195149616.001.0001/acprof-9780195149616
21. de Koning HJ. Assessment of nationwide cancer-screening programmes. The Lancet. 2000 Jan 8;355(9198):80–1.
22. Raffle AE, Alden B, Quinn M, Babb PJ, Brett MT. Outcomes of screening to prevent cancer: analysis of cumulative incidence of cervical abnormality and modelling of cases and deaths prevented. BMJ. 2003 Apr 26;326(7395):901.
23. Ioannidis JP, Lau J. Completeness of safety reporting in randomized trials: an evaluation of 7 medical areas. JAMA. 2001 Jan 24;285(4):437–43.
24. Wegwarth O, Gigerenzer G. "There is nothing to worry about": Gynecologists' counseling on mammography. Patient Education and Counseling. 2011 Aug;84(2):251–6.
25. Hardcastle JD, Chamberlain JO, Robinson MH, Moss SM, Amar SS, Balfour TW, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet. 1996 Nov 30;348(9040):1472–7.
26. Kronborg O, Fenger C, Olsen J, Jørgensen OD, Søndergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet. 1996 Nov 30;348(9040):1467–71.
27. Kewenter J, Brevinge H, Engaråas B, Haglind E, Ahrén C. Results of screening, rescreening, and follow-up in a prospective randomized study for detection of colorectal cancer by fecal occult blood testing. Results for 68,308 subjects. Scand. J. Gastroenterol. 1994 May;29(5):468–73.
28. National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events, Version 4.03 [Internet]. U.S. Department of Health and Human Services; 2010 [cited 2011 Aug 2]. Available from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf
29. Papanikolaou PN, Ioannidis JPA. Availability of large-scale evidence on specific harms from systematic reviews of randomized trials. Am. J. Med. 2004 Oct 15;117(8):582–9.
30. Chou R, Aronson N, Atkins D, Ismaila AS, Santaguida P, Smith DH, et al. AHRQ Series Paper 4: Assessing harms when comparing medical interventions: AHRQ and the Effective Health-Care Program. Journal of Clinical Epidemiology. 2010 May;63(5):502–12.
31. Ioannidis JPA, Evans SJW, Gøtzsche PC, O'Neill RT, Altman DG, Schulz K, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. Ann. Intern. Med. 2004 Nov 16;141(10):781–8.
32. Ioannidis JP, Contopoulos-Ioannidis DG. Reporting of safety data from randomised trials. Lancet. 1998 Nov 28;352(9142):1752–3.
33. Edwards JE, McQuay HJ, Moore RA, Collins SL. Reporting of adverse effects in clinical trials should be improved: lessons from acute postoperative pain. J Pain Symptom Manage. 1999 Dec;18(6):427–37.
34. Loke YK, Derry S. Reporting of adverse drug reactions in randomised controlled trials - a systematic survey. BMC Clin Pharmacol. 2001;1:3.
35. Bryant J, Loveman E, Cave C, Chase D, Milne R. Endocrinology trial design: adverse event reporting in randomised controlled trials of recombinant human GH in GH-deficient adults. J.

Endocrinol. 2002 Nov;175(2):545–52.
36. Martin RCG 2nd, Brennan MF, Jaques DP. Quality of complication reporting in the surgical literature. Ann. Surg. 2002 Jun;235(6):803–13.
37. Papanikolaou PN, Churchill R, Wahlbeck K, Ioannidis JPA. Safety reporting in randomized trials of mental health interventions. Am J Psychiatry. 2004 Sep;161(9):1692–7.
38. Ethgen M, Boutron I, Baron G, Giraudeau B, Sibilia J, Ravaud P. Reporting of harm in randomized, controlled trials of nonpharmacologic treatment for rheumatic disease. Ann. Intern. Med. 2005 Jul 5;143(1):20–5.
39. Lee P, Fischer H, Rochon P, Gill S, Herrmann N, Bell C, et al. Published randomized controlled trials of drug therapy for dementia often lack complete data on harm. Journal of Clinical Epidemiology. 2008 Nov;61(11):1152–60.
40. Pitrou I, Boutron I, Ahmad N, Ravaud P. Reporting of safety results in published reports of randomized controlled trials. Arch. Intern. Med. 2009 Oct 26;169(19):1756–61.
41. Yazici Y, Yazici H. A survey of inclusion of the time element when reporting adverse effects in randomised controlled trials of cyclo-oxygenase-2 and tumour necrosis factor inhibitors. Annals of the Rheumatic Diseases. 2006 Jun;66(1):124–7.
42. Nuovo J, Sather C. Reporting adverse events in randomized controlled trials. Pharmacoepidemiol Drug Saf. 2007 Mar;16(3):349–51.
43. Higgins J, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions [Internet]. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration; 2011 [cited 2012 Apr 12]. Available from: www.cochrane-handbook.org
44. Scottish Intercollegiate Guidelines Network. Search Filters [Internet]. Search Filters. 2012 [cited 2012 Apr 27]. Available from: http://www.sign.ac.uk/methodology/filters.html#random

Search strategies for CENTRAL (The Cochrane Library Website)

Common

#1	MeSH descriptor Mass Screening explode all trees
#2	MeSH descriptor Population Surveillance explode all trees
#3	(screen* or test* or (population* NEAR/2 surveillance) or (early NEAR/3 detect*) or (early NEAR/3 prevent*)):ti,kw,ab
#4	(#1 OR #2 OR #3)

Lung cancer screening with computed tomography

#5	MeSH descriptor Lung Neoplasms explode all trees
#6	((lung* or pulmon* or bronch*) NEAR/10 (tumor* or tumour* or cancer or neoplas* or carcinoma* or adenocarcinoma* or squamous or (oat NEAR/2 cell) or (small NEAR/2 cell))):ti,kw,ab
#7	(#5 OR #6)
#8	MeSH descriptor Tomography, Spiral Computed explode all trees
#9	((comput* NEAR/2 tomogra*) or CT):ti,kw,ab
#10	(#8 OR #9)
#11	(#4 AND #7 AND #10)

Colorectal cancer screening with gastrointestinal endoscopy

#5	MeSH descriptor Endoscopy explode all trees
#6	MeSH descriptor Colonoscopy explode all trees
#7	MeSH descriptor Sigmoidoscopy explode all trees
#8	MeSH descriptor Proctoscopy explode all trees
#9	(endoscop* or proctoscop* or colonoscop* or sigmoidoscop* or rectosigmoidoscop* or proctosigmoidoscop* or fibrosigmoidoscop* or COL or SIG or FSIG) or (flex* near/3 sig*):ti,ab,kw
#10	(#5 OR #6 OR #7 OR #8 OR #9)
#11	MeSH descriptor Colorectal Neoplasms explode all trees
#12	MeSH descriptor Colonic Neoplasms explode all trees
#13	MeSH descriptor Rectal Neoplasms explode all trees
#14	(colorectal* or CRC or colon* or bowel* or intestine* or large intestine* or rectal or rectum or sigmoid or anal or anus) and (cancer or neoplasm* or malign* or tumor or tumour* or carcinom* or sarcom* or adenocarcinom* or adeno?carcinom* or adenom* or lesion*):ti,ab,kw
#15	(#11 OR #12 OR #13 OR #14)
#16	(#4 AND #10 AND #15)

Colorectal cancer screening with computed tomography

#5	MeSH descriptor Colorectal Neoplasms explode all trees
#6	MeSH descriptor Colonic Neoplasms explode all trees
#7	MeSH descriptor Rectal Neoplasms explode all trees
#8	(colorectal* or CRC or colon* or bowel* or intestine* or large intestine* or rectal or rectum or sigmoid or anal or anus) and (cancer or neoplasm* or malign* or tumor or tumour* or carcinom* or sarcom* or adenocarcinom* or adeno?carcinom* or adenom* or lesion*):ti,ab,kw
#9	(#5 OR #6 OR #7 OR #8)
#10	MeSH descriptor Tomography, Spiral Computed explode all trees
#11	(((CT or (comput* tomogra*)) NEAR/10 (colorectal* or CRC or colon or colonic or bowel* or intestine or (large NEAR/2 intestine) or rectal or rectum or sigmoid or anal or anus)) or (virtual NEAR/2 colono*)):ti,ab,kw
#12	(#10 OR #11)
#13	(#4 AND #9 AND #12)

Ovarian cancer screening

#5	MeSH descriptor Ovarian Neoplasms explode all trees
#6	ovar* and (cancer* or carcinoma* or neoplasm* or tumor* or tumour* or malignan*):ti,ab,kw
#7	(#5 OR #6)
#8	(#4 AND #7)

Appendix 2b: Protocol amendment

What is the frequency of adverse event reporting in cancer screening trials: a literature survey

Protocol amendment

The search strategy described in the original protocol missed articles for some of the trials that will be included in the analysis. Failing to include these articles may lead to underestimation of the percentage of trials reporting harm-related outcomes. Hence, a protocol amendment describing a revised search strategy is presented here.

Methods

Revised search strategies

Electronic searches

We will perform electronic searches in the Cochrane Central Register of Controlled Trials (The Cochrane Library), Ovid MEDLINE, Ovid MEDLINE In-process & other non-indexed citations, and EMBASE (Ovid).

Search strategies in the Cochrane Central Register of Controlled Trials will use a combination of controlled vocabulary and free-text terms. Whenever a screening technology has been reviewed in a Cochrane Systematic Review, we will reproduce the search strategy described in the review. If a Cochrane Review is not available, the search strategy will be composed of three dimensions: cancer-related terms, technology-related terms, screening-related terms.

The search strategies in MEDLINE and EMBASE will include the names of trials known to us, or the names of the principal investigators of the trials. There will be no language or publication status restrictions.

Details of the search strategies are provided in the Appendix.

Grey literature, journals and conference proceedings, and other sources

Given that the aim is to assess the adequacy of harm reporting in clinical trials, no contact will be made with the study authors and no other sources of data will be sought.

Search strategies for CENTRAL (The Cochrane Library Website) 25/04/2012

Common

#1	MeSH descriptor Mass Screening explode all trees
#2	MeSH descriptor Population Surveillance explode all trees
#3	(screen* or test* or (population* NEAR/2 surveillance) or (early NEAR/3 detect*) or (early NEAR/3 prevent*)):ti,kw,ab
#4	(#1 OR #2 OR #3)

Lung cancer screening with computed tomography

#5	MeSH descriptor Lung Neoplasms explode all trees
#6	((lung* or pulmon* or bronch*) NEAR/10 (tumor* or tumour* or cancer or neoplas* or carcinoma* or adenocarcinoma* or squamous or (oat NEAR/2 cell) or (small NEAR/2 cell))):ti,kw,ab
#7	(#5 OR #6)
#8	MeSH descriptor Tomography, Spiral Computed explode all trees
#9	((comput* NEAR/2 tomogra*) or CT):ti,kw,ab
#10	(#8 OR #9)
#11	(#4 AND #7 AND #10)

Colorectal cancer screening with gastrointestinal endoscopy

#5	MeSH descriptor Endoscopy explode all trees
#6	MeSH descriptor Colonoscopy explode all trees
#7	MeSH descriptor Sigmoidoscopy explode all trees
#8	MeSH descriptor Proctoscopy explode all trees
#9	(endoscop* or proctoscop* or colonoscop* or sigmoidoscop* or rectosigmoidoscop* or proctosigmoidoscop* or fibrosigmoidoscop* or COL or SIG or FSIG) or (flex* near/3 sig*):ti,ab,kw
#10	(#5 OR #6 OR #7 OR #8 OR #9)
#11	MeSH descriptor Colorectal Neoplasms explode all trees
#12	MeSH descriptor Colonic Neoplasms explode all trees
#13	MeSH descriptor Rectal Neoplasms explode all trees
#14	(colorectal* or CRC or colon* or bowel* or intestine* or large intestine* or rectal or rectum or sigmoid or anal or anus) and (cancer or neoplasm* or malign* or tumor or tumour* or carcinom* or sarcom* or adenocarcinom* or adeno?carcinom* or adenom* or lesion*):ti,ab,kw
#15	(#11 OR #12 OR #13 OR #14)
#16	(#4 AND #10 AND #15)

Colorectal cancer screening with computed tomography

#5	MeSH descriptor Colorectal Neoplasms explode all trees
#6	MeSH descriptor Colonic Neoplasms explode all trees
#7	MeSH descriptor Rectal Neoplasms explode all trees
#8	(colorectal* or CRC or colon* or bowel* or intestine* or large intestine* or rectal or rectum or sigmoid or anal or anus) and (cancer or neoplasm* or malign* or tumor or tumour* or carcinom* or sarcom* or adenocarcinom* or adeno?carcinom* or adenom* or lesion*):ti,ab,kw
#9	(#5 OR #6 OR #7 OR #8)
#10	MeSH descriptor Tomography, Spiral Computed explode all trees
#11	(((CT or (comput* tomogra*)) NEAR/10 (colorectal* or CRC or colon or colonic or bowel* or intestine or (large NEAR/2 intestine) or rectal or rectum or sigmoid or anal or anus)) or (virtual NEAR/2 colono*)):ti,ab,kw
#12	(#10 OR #11)
#13	(#4 AND #9 AND #12)

Ovarian cancer screening

#5	MeSH descriptor Ovarian Neoplasms explode all trees
#6	ovar* and (cancer* or carcinoma* or neoplasm* or tumor* or tumour* or malignan*):ti,ab,kw
#7	(#5 OR #6)
#8	(#4 AND #7)

Search strategies for EMBASE (Ovid) and Ovid MEDLINE and Ovid MEDLINE In-process & other non-indexed citations

1 (Pisani P* or Laudico A*).au. and clinical breast examination.ti,ab,kw.
2 (Sankaranarayanan R* or Mathew B*).au. and clinical breast examination.ti,ab,kw.
3 (Mittra I* or Shastri S*).au. and clinical breast examination.ti,ab,kw.
4 (Semiglazov V* or Moiseenko V*).au. and self examination.ti,ab,kw.
5 (Thomas D* or Dao-Li G*).au. and self examination.ti,ab,kw.
6 (Miller AB or Boulos S*).au. and (breast examination or self examination).ti,ab,kw.
7 1 or 2 or 3 or 4 or 5 or 6
8 (Kubik A* or Parkin D*).au. and lung cancer.ti,ab,kw. and screen*.ti,ab,kw.
9 Wilde J*.au. and lung cancer.ti,ab,kw. and screen*.ti,ab,kw.
10 (Frost J* or Stitik F*).au. and lung cancer.ti,ab,kw. and screen*.ti,ab,kw.
11 ((Dales L* or Friedman G*).au. or multiphasic.ti,ab,kw.) and lung cancer.ti,ab,kw. and screen*.ti,ab,kw.
12 (Fontana R* or Marcus P*).au. and lung cancer.ti,ab,kw. and screen*.ti,ab,kw.
13 "Mayo Lung Project".ti,ab,kw.
14 (Flehinger B* or Melamed M*).au. and lung cancer.ti,ab,kw. and screen*.ti,ab,kw.
15 Brett G*.au. and lung cancer.ti,ab,kw. and screen*.ti,ab,kw.
16 (Oken M* or Pinsky P*).au. and lung cancer.ti,ab,kw. and screen*.ti,ab,kw.
17 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18 ((Selby J* or Collen M*).au. or multiphasic.ti,ab,kw.) and (screen* adj5 sigmoidoscopy).ti,ab,kw
19 (Norwegian Colorectal Cancer Prevention or NORCCAP).af.
20 (Hoff G* or Bretthauer M*).au. and (screen* adj5 sigmoidoscopy).ti,ab,kw.
21 ((Screening for Colon Rectum or SCORE) and (screen* adj5 sigmoidoscopy)).af.
22 (Segnan N* or Senore C*).au. and (screen* adj5 sigmoidoscopy).ti,ab,kw.
23 (colonprev.ti,au,ab,kw. or (Quintero E or Gonzalez-Navarro A).au.) and (screen* or cribado).ti,ab,kw
24 (Hoff G* or Thiis-Evensen E*).au. and (screen* adj5 sigmoidoscopy).ti,ab,kw.
25 Telemark Polyp Study.ti,ab,kw.
26 Atkin W*.au. and (screen* adj5 sigmoidoscopy).ti,ab,kw
27 ((UK or U K or United Kingdom) and Flexible Sigmoidoscopy Trial).af.
28 (Schoen R* or Weissfeld J*).au. and (screen* adj5 sigmoidoscopy).ti,ab,kw.
29 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30 (J*rgensen O* or Kronborg O*).au. and (f*cal occult blood or FOBT).ti,ab,kw.
31 (Kewenter J* or Brevinge H*).au. and (f*cal occult blood or FOBT).ti,ab,kw.
32 (Mandel J* or Church T*).au. and (f*cal occult blood or FOBT).ti,ab,kw.
33 (Hardcastle JD or Scholefield JH).au. and (f*cal occult blood or FOBT).ti,ab,kw.
34 (Niv Y or Tamir A).au. and (f*cal occult blood or FOBT).ti,ab,kw.
35 (Malila N* or Paimela H*).au. and (f*cal occult blood test or FOBT).ti,ab,kw.
36 (Zheng S* or Zhang S*).au. and colorectal cancer.ti,ab,kw. and screen*.ti,ab,kw.
37 30 or 31 or 32 or 33 or 34 or 35 or 36
38 (Chen JG or Zhu YR).au. and (liver cancer or hepatoma or hepatocellular).ti,ab,kw. and screen*.ti,ab,kw.

39 (Sherman M or Lee C).au. and (liver cancer or hepatoma or hepatocellular).ti,ab,kw. and screen*.ti,ab,kw.
40 (Yang B or Zhang B*).au. and (liver cancer or hepatoma or hepatocellular).ti,ab,kw. and screen*.ti,ab,kw.
41 38 or 39 or 40
42 DANTE.ti,ab,kw,au. and (lung or screen*).ti,ab,kw.
43 (Infante M* or Ravasi G*).au. and lung cancer.ti,ab,kw. and screen*.ti,ab,kw.
44 (DLCST or Danish Lung Cancer Screening Trial).ti,ab,kw,au.
45 (Pedersen J* or Dirksen A*).au. and lung cancer.ti,ab,kw. and screen*.ti,ab,kw.
46 ITALUNG.ti,ab,kw,au.
47 (Pegna A* or Paci E*).au. and lung cancer.ti,ab,kw. and screen*.ti,ab,kw.
48 (LUSI or "Lung Cancer Screening Intervention trial").ti,ab,kw,au.
49 (Becker N* or Delorme S*).au. and lung cancer.ti,ab,kw. and screen*.ti,ab,kw.
50 Multicentric Italian Lung Detection.ti,ab,kw,au. or MILD.au. or (MILD and (lung adj2 screen*)).ti,ab.
51 (Marchiano A* or Pastorino U*).au. and lung cancer.ti,ab,kw. and screen*.ti,ab,kw.
52 (NELSON.ti,ab,kw,au. and (lung or screen*).ti,ab,kw.) or ("Dutch-Belgian randomized lung cancer screening trial" or "Nederlands-Leuvens Longkanker Screenings Onderzoek" or "Dutch Belgian randomized lung cancer screening trial" or "Nederlands Leuvens Longkanker Screenings Onderzoek").ti,ab,kw,au.
53 (de Koning R* or van Klaveren R*).au. and lung cancer.ti,ab,kw. and screen*.ti,ab,kw.
54 (NLST or "National Lung Screening Trial").ti,ab,kw,au.
55 (Aberle D* or Adams A*).au. and lung cancer.ti,ab,kw. and screen*.ti,ab,kw.
56 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55
57 (Baines C* or Miller AB).au. and mammog*.ti,ab,kw.
58 (Alexander F* or Chamberlain J).au and mammog*.ti,ab,kw.
59 (Bjurstam N* or Nystrom L*).au and mammog*.ti,ab,kw.
60 (Andersson I* or Janzon L).au. and mammog*.ti,ab,kw.
61 (Shapiro S or Strax P).au and mammog*.ti,ab,kw
62 (Arnesson LG or Fagerberg G).au and mammog*.ti,ab,kw
63 (Frisell J* or Lindbrink E).au and mammog*.ti,ab,kw
64 (Tabar L* or Duffy S*).au and mammog*.ti,ab,kw
65 (Moss S* or Cuckle H).au and mammog*.ti,ab,kw
66 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65
67 (Sankaranarayanan R or Ramadas K).au. and oral cancer.ti,ab,kw. and screen*.ti,ab,kw.
68 (Kobayashi H* or Kitanaka T*).au. and ovarian cancer.ti,ab,kw. and screen*.ti,ab,kw.
69 (UK Collaborative Trial of Ovarian Cancer Screening or UKCTOCS).af.
70 (Menon U* or Jacobs I*).au. and ovarian cancer.ti,ab,kw. and screen*.ti,ab,kw.
71 (Buys S* or Partridge E*).au. and ovarian cancer.ti,ab,kw. and screen*.ti,ab,kw.
72 68 or 69 or 70 or 71
73 (ERSPC or European Randomised Study of Screening for Prostate Cancer).af.
74 (Schroder F* or Hugosson J*).au and prostate cancer.ti,ab,kw. and screen*.ti,ab,kw.
75 (Sandblom G* or Varenhorst E*).au. and prostate cancer.ti,ab,kw. and screen*.ti,ab,kw.
76 (Labrie F* or Levesque J*).au. and prostate cancer.ti,ab,kw. and screen*.ti,ab,kw.
77 (Kjellman A* or Gustafsson O*).au. and prostate cancer.ti,ab,kw. and screen*.ti,ab,kw.
78 (Comparison Arm for ProtecT or (prostate testing for cancer and treatment)).ti,ab.
79 Protect.ti,ab,kw,au. and prostate.ti,ab,kw. and screen*.ti,ab,kw.
80 (Martin R* or Hamdy F*).au and prostate cancer.ti,ab,kw. and screen*.ti,ab,kw.

81 (Andriole G* or Crawford E*).au and prostate cancer.ti,ab,kw. and screen*.ti,ab,kw.
82 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81
83 (Prostate, Lung, Colorectal and Ovarian).ti,ab,kw. or PLCO.ti,ab,kw,au.
84 7 or 17 or 29 or 37 or 41 or 56 or 66 or 67 or 72 or 82 or 83

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86 84 not 85

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86 84 not 85